

Delving into cornerstones of hypersensitivity to antineoplastic and biological agents: value of diagnostic tools prior to desensitization

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Abstract

Background: Evidence regarding drug provocation test (DPT) with antineoplastic and biological agents is scarce. Our aim was to assess the usefulness of including DPT as a paramount gold standard diagnostic tool (prior to desensitization).

Methods: Prospective, observational, longitudinal study with patients who, during a 3-year period, were referred to the Desensitization Program at Ramon y Cajal University Hospital. Patients underwent a structured diagnostic protocol by means of anamnesis, skin tests (ST), risk assessment, and DPT. Oxaliplatin-specific IgE was determined in oxaliplatin-reactive patients (who underwent DPT regardless of oxaliplatin-specific IgE results). Univariate analysis and multivariate analysis were used to identify predictors of the final diagnosis among several variables.

Results: A total of 186 patients were assessed. A total of 104 (56%) patients underwent DPT. Sixty-four percent of all DPTs were negative (i.e., hypersensitivity was excluded). Sensitivity for oxaliplatin-specific IgE (0.35 UI/l cutoff point) was 34%, specificity 90.3%, negative predictive value 45.9%, positive predictive value 85%, negative likelihood ratio 0.7, and positive likelihood ratio 3.5.

Conclusions: These are the first reported data based on more than 100 DPTs with antineoplastic and biological agents (paclitaxel, oxaliplatin, rituximab, infliximab, irinotecan, and other drugs). Implementation of DPT in diagnostic protocols helps exclude hypersensitivity (in 36% of all referred patients), and avoids unnecessary desensitizations in nonhypersensitive patients (30–56% of patients, depending on culprit-drug). Drug provocation test is vital to validate diagnostic tools; consequently, quality data are shown on oxaliplatin-specific IgE and oxaliplatin-ST in the largest series of oxaliplatin-reactive patients reported to date (74 oxaliplatin-reactive patients). Identifying phenotypes and predictors of a diagnosis of hypersensitivity may be helpful for tailored plans.

Drug provocation test (DPT), or graded/diagnostic challenge, is the controlled administration of a drug to study hypersensitivity reactions (HSRs), and it is considered to be the gold standard to establish or exclude the diagnosis of hypersensitivity (1–3).

Although DPT with antineoplastic and biological agents is considered in some review articles (4–6), previous works do not clearly show data about DPT with these drugs (7–11), so evidence regarding this topic is scarce.

Drug desensitization is a therapeutic technique which induces a temporary state of tolerance to a drug responsible

for a proven HSR (12). An international consensus (12) as well as previous articles by our group (13–17) recommends diagnostic DPT (whenever feasible) prior to drug desensitization.

The primary endpoint of this study is to assess the usefulness of including DPT as a paramount gold standard diagnostic tool to rule out the diagnosis of hypersensitivity to antineoplastic and biological agents in our population.

Secondary endpoint is to calculate sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratios for skin tests (ST) and oxaliplatin-specific IgE in our oxaliplatin-reactive population.

Additional endpoints are to identify characteristics of patients, drugs, or reactions that could be acting as risk factors or may need tailored plans.

Methods

Patient population

We carried out a prospective, observational, longitudinal study with the patients who, during a 3-year period (between January 2011 and January 2014), had suffered HSRs to antineoplastic and biological agents in the Ramon y Cajal University Hospital (RCUH) and had been referred to our Allergy Division's Desensitization Program.

Informed consent statement

The RCUH Ethics Committee approved the study protocol and validated informed consents that required signing by patient, allergist, and referring physician.

Diagnostic protocol: anamnesis/initial reaction

Signs and symptoms from initial reactions and characteristics of patients were collected as in previous articles by our group (13–17). Additionally, oxaliplatin-specific IgE was determined by ImmunoCAP® (Thermo Fisher Scientific Waltham, MA USA) in all oxaliplatin-reactive patients. Regarding severity of the initial reaction, patients were classified in three groups according to a previous classification published by Brown (18): grade 1 or mild reactions (skin and subcutaneous tissues only), defined by generalized erythema, urticaria, periorbital edema, or angioedema; grade 2 or moderate reactions (features suggesting respiratory, cardiovascular, or gastrointestinal involvement), defined by dyspnea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain; and grade 3 or severe reactions (hypoxia, hypotension, or neurologic compromise), defined by cyanosis or $\text{SpO}_2 \leq 92\%$ at any stage, hypotension (systolic blood pressure <90 mmHg in adults), confusion, collapse, loss of consciousness, or incontinence.

Diagnostic protocol: risk assessment

As in previous works by our group (13–17), patients were classified into two groups (high-risk or medium-/low-risk) according to their risk assessment.

Diagnostic protocol: skin testing

Trained personnel in adequate settings performed and assessed ST on all referred patients according to previous articles (12–17, 19). ST concentrations used by our group (5–8, 13, 14) are shown in Table 1.

Diagnostic protocol: drug provocation test

Drug provocation test was not performed in patients whose treatment was to be discontinued or changed to an alterna-

Table 1 Concentrations used for skin testing with antineoplastic and biological agents in patients referred to our Desensitization Program

Drugs	Prick test concentration (mg/ml)	Intradermal test concentrations (mg/ml)
Carboplatin	10	1 and 10
Cisplatin	1	0.1 and 1
Oxaliplatin	5	0.5 and 5
Paclitaxel	6	1 and 6
Docetaxel	10	1 and 10
Rituximab	10	1 and 10
Infliximab	10	1 and 10
Cetuximab	5	0.5 and 5
Bevacizumab	25	2.5 and 25
Irinotecan	20	2 and 20
Gemcitabine	38	3.8 and 38
Cyclophosphamide	10	1 and 10
Anakinra	150	15 and 150
Leucovorin	10	10 and 1

As in previous studies (13–17), drugs were prepared by the Pharmacy Department Cytotoxic Unit. For skin prick test, a drop of the drug at the maximal concentration was applied to the volar surface of the forearm by the use of a skin prick test lancet. If prick test were negative, for intradermal injections, 0.03 ml of the drug (first at minimal concentration, and, if negative, maximal concentration) was injected. A positive reaction was defined as a wheal with a diameter at least 3 mm larger than that produced by a negative control (dilutor). Histamine (10 mg/ml) was used as a positive control. As in previous studies (13–17), skin tests were performed at least 2 weeks after initial reaction, to avoid false-negative results. These concentrations were tested in at least 10 non-reactive patients to prove them nonirritant.

tive therapeutic option. Consequently, an additional informed consent confirming indication for treatment with the culprit-drug (signed by patients and referring physicians) was requested.

Patients with late reactions occurring beyond 48 h after infusion, severe immunocytotoxic reactions, vasculitis, bullous skin diseases such as Stevens–Johnson syndrome (SJS)/toxic epidermal necrosis (TEN), or drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome (DIHS) were excluded from DPT (12, 13).

Patients in the medium-/low-risk group who presented with reactions consistent with immediate-type HSRs during or shortly after (≤ 48 h) the culprit-drug infusion and who signed the informed consents (after in-depth explanation of their individual risk–benefit assessment) were subjected to DPT. The patient's next scheduled treatment was used as DPT (avoiding therefore problems such as delays or overdose), meaning that most patients (with some exceptions) were to be scheduled for DPT approximately 2–3 weeks after the initial reaction (depending on chemotherapy regimes and patient individual treatments). DPT was undergone in Medical Intensive Care Unit beds assigned to the Desensitization Program (1, 13–17).

Table 2 Comparisons between data from the anamnesis/initial reaction and the patient's final diagnosis (FD)

Univariate analysis				
Characteristics	Positive (<i>n</i> = 78)	Negative (<i>n</i> = 65)	Unconfirmed (<i>n</i> = 43)	<i>P</i> value
Gender				
Female	45	38	27	0.85
Male	33	27	16	
Atopy				
Yes	21	13	16	0.14
No	57	52	27	
Drug allergy				
Yes	14	12	11	0.57
No	64	53	32	
Severity (Brown)				
Grade 1	29	33	14	0.06
Grade 2	33	26	16	
Grade 3	15	6	13	
Elapsed time				
<15 min	30	23	19	0.59
15–60 min	34	26	13	
>60 min	14	16	11	
Previous reactions				
Yes	28	11	10	0.03
No	50	54	33	
Retreatment				
No	57	54	32	0.34
Yes	21	11	11	
Cutaneous				
Yes	67	43	36	0.01
No	11	22	7	
Gastrointestinal				
Yes	23	5	9	0.005
No	55	60	34	
Respiratory				
Yes	37	25	25	0.13
No	41	40	18	
Cardiovascular				
Yes	27	9	20	0.001
No	51	56	23	
Neuromuscular				
Yes	5	4	4	0.79
No	73	61	39	
Fever/chills				
Yes	15	12	9	0.95
No	63	53	34	
Culprit-drug				
Platins	50	31	14	0.004
Taxanes	17	17	9	
Biologicals	7	9	14	
Other	4	8	6	
Multivariate analysis				
Association variable—final diagnosis	RR	95% CI	<i>P</i> value	
Culprit-drugs				
Platins – positive	2.09	1.03–2.53	0.04	
Biologicals – unconfirmed	2.31	1.21–9.83	0.02	

Table 2 (continued)

Multivariate analysis			
Association variable—final diagnosis	RR	95% CI	<i>P</i> value
Previous reactions			
Yes – positive	3.99	1.69–9.44	0.002
Cutaneous			
Yes – positive	3.46	1.41–8.47	0.007
Gastrointestinal			
Yes – positive	2.87	1.69–16.07	0.004
Cardiovascular			
Yes – unconfirmed	3.15	1.79–12.28	0.002

Univariate analysis with the chi-square test was used for determining significant associations between final diagnosis (FD) and the following anamnesis/initial reaction variables: severity (mild, moderate, or severe), gender, elapsed time from drug administration to HSR onset (≤ 15 min; > 15 min; ≤ 60 min; > 60 min), previous reactions (generally unnoticed/overlooked mild reactions during previous administrations of the same culprit-drug), confirmed drug allergy, culprit-drug (platins, taxanes, biological agents, other drugs), atopy, 'retreatment' (starting new treatment with an antineoplastic drug the patient had previously received for a period of time, but had discontinued for a period over 12 months), and symptoms (cutaneous, respiratory, cardiovascular, gastrointestinal, neurologic/muscular, and fever/chills).

Multivariate analysis with multinomial logistic regression was used to confirm the importance of possible associations and identify significant predictors of the FD. Of all multivariate comparisons, only those which show a significant association as predictors of FD are presented here.

Drug provocation test consisted in administering the desired full dose of the culprit-drug according to manufacturer instructions. Infusion rates were the same as standard regimes. No additional premedication was used for the procedure (except for standard premedications according to manufacturer/institutional protocols). Beta-blockers and ACE inhibitors were held prior to the procedure (1, 13–17, 20). To keep standard regimes unaltered, additional required medications (other antineoplastics, leucovorin, etc.) were also administered as prescribed by referring physician.

Drug provocation test was considered positive when it reproduced the original symptoms or showed an objective HSR (1, 13–17). In case of a positive DPT, the infusion was held and the HSR was treated accordingly. Once symptoms were controlled and the patient was asymptomatic, the infusion was immediately (approximately within 30 min after the HSR) restarted at 1/4 of the final infusion rate for 15 min, and then increased to 1/2 of the initial infusion rate until all the medication was administered ('restart protocol').

Whenever needed, provocations with other drugs such as premedications, concomitant drugs (14), or additional antineoplastic or biological agents possibly involved in the initial reactions were performed before DPT with the culprit-drug.

All patients with a negative DPT were followed during subsequent standard drug administrations.

Table 3 Characteristics of the 186 patients referred to our Desensitization Program over a 3-year period, and features of their initial reactions

Characteristics	Number of patients (percentage)
Primary diagnoses	
Colorectal cancer	86/186 (46)
Breast cancer	34/186 (18)
Ovarian cancer	19/186 (10)
Non-Hodgkin lymphoma	17/186 (9)
Pancreatic cancer	7/186 (4)
Gastric cancer	5/186 (3)
Lung cancer	4/186 (2)
Crohn's disease	4/186 (2)
Rheumatoid Arthritis	3/186 (2)
Cervical cancer	3/186 (2)
Laryngeal cancer	2/186 (1)
Dermatomyositis	1/186 (0.5)
Familial Mediterranean fever	1/186 (0.5)
Culprit-drug	
Platins	95/186 (51)
Oxaliplatin	74/186 (40)
Carboplatin	16/186 (9)
Cisplatin	5/186 (3)
Taxanes	43/186 (23)
Paclitaxel	39/186 (21)
Docetaxel	4/186 (2)
Biological agents	30/186 (16)
Rituximab	17/186 (9)
Infliximab	7/186 (4)
Cetuximab	3/186 (2)
Bevacizumab	2/186 (1)
Anakinra	1/186 (0.5)
Other drugs	18/186 (10)
Irinotecan	11/186 (6)
Liposomal doxorubicine	4/186 (2)
Cyclophosphamide	2/186 (1)
Gemcitabine	1/186 (0.5)
History of atopy	51/186 (27)
History of confirmed drug allergy	38/186 (20)

Characteristics	Clinical features and severity of initial reactions			
	Platins (n = 95)	Taxanes (n = 43)	Biologicals (n = 30)	Other (n = 18)
Symptoms, %				
Cutaneous	71	90	77	72
Cardiovascular	34	33	33	6
Respiratory	47	55	60	22
Gastrointestinal	26	10	23	11
Neuromuscular	16	30	13	6
Fever/chills	21	5	27	28
Severity (Brown), %				
Grade 1	39	37	37	61
Grade 2	40	37	50	28
Grade 3	21	26	13	11

Table 4 Outcomes of 104 drug provocation tests (DPTs) with anti-neoplastic agents in 186 patients referred during a 3-year period to our Desensitization Program

	Positive, % (n = 37)	Negative, % (n = 67)	Not undergone, % (n = 82)
Platins (n = 95)	21	32	44
Taxanes (n = 43)	21	40	40
Biologicals (n = 30)	13	30	57
Other (n = 18)	22	56	22
All (n = 186)	20	36	44
Reasons for not undergoing DPT, %			
	Did not consent DPT (n = 41)	High-risk patients (n = 21)	Alternative therapy (n = 20)
Not undergone DPTs (n = 82)	50	26	24
Severity of HSRs during positive DPTs (Brown's classification), %			
	Mild (n = 18)	Moderate (n = 15)	Severe (n = 4)
Positive DPTs (n = 37)	49	41	11

HSR, hypersensitivity reaction; ST, skin tests; DPT, drug provocation test.

Final diagnosis

Patient's final diagnosis (FD) has been defined as 'positive' (positive ST and/or positive DPT) or 'negative' (negative DPT) in previous works by our group (13–17). Associations between FD and several variables were studied (Table 2).

Results

Patient characteristics

A total of 186 patients were referred to our Desensitization Program during a 3-year period. Mean age was 59 years (ranging from 9 to 81 years). Most patients were being treated for malignancy (177/186), but some patients were being treated for inflammatory disorders (9/186). More data are shown on Table 3.

Initial reaction

All reactions occurred within 48 h after culprit-drug administration, and all were consistent with immediate-type HSRs. We found no patients presenting with delayed-/late-type HSRs. Initial reaction was moderate or severe (grade 2 or 3)

in 59% (110/186), and 41% (76/186) of patients suffered a mild initial reaction (grade 1). Characteristics of initial reactions are shown in Table 3.

DPT outcomes

A total of 104 patients (56% of the total 186) underwent DPT with the culprit-drug: 67 of 104 (64% of all DPTs) were negative, and 37 of 104 (36% of all DPTs) were positive. Results are shown in further detail in Table 4.

Of the 37 patients with a positive DPT, four patients suffered a severe reaction: one oxaliplatin-reactive patient (severe anaphylaxis consisting on urticaria, dyspnea, wheeze, $\text{SpO}_2 \leq 92\%$, and hypotension); two paclitaxel-reactive patients (both presenting with erythema, severe back pain, and hypotension); and one rituximab-reactive patient (presenting with urticaria, dyspnea with $\text{SpO}_2 \leq 92\%$, throat tightness, abdominal pain, and vomiting). All of them needed adrenaline intramuscularly (as well as treatment with intravenous corticosteroids, intravenous antihistamines, oxygen, and nebulized bronchodilators), and recovered within 30 min after reaction.

Patients with a negative DPT were followed during their next administrations (up to eight additional administrations). One paclitaxel-reactive patient showed another HSR after three administrations, but it was finally related to another culprit-drug. Two oxaliplatin-reactive patients presented with HSRs during follow-up, and both became 'positive converters' (with positive ST and oxaliplatin-specific IgE; see Table 5).

Interestingly, seven patients with positive ST showed a negative DPT and experienced no reactions during the follow-up: four paclitaxel-reactive patients with positive intradermal test (ID) to 6 mg/ml concentration; two oxaliplatin-reactive patients with positive ID to 5 mg/ml; and one carboplatin-reactive patient with ID to 10 mg/ml.

Additional DPTs (with concomitant drugs, premedications, etc.) were needed in most cases, but they were shown to be especially useful when facing chemotherapy regimes including leucovorin. Leucovorin is usually administered simultaneously with other drugs (e.g., oxaliplatin, irinotecan) (14). During this 3-year period, leucovorin was found to be the causal agent for the HSR in 11 of 186 patients (in whom DPT with the referral 'culprit-drug' was confirmed as negative).

All reactive patients were subjected to our 'restart protocol' for positive DPTs and all of them showed good tolerance to it, except for one paclitaxel-reactive patient who suffered a severe reaction during DPT and then persistent erythema and dyspnea when paclitaxel was restarted, and one oxaliplatin-reactive patient who suffered fever/chills and back pain during DPT, and also during restart.

Associations between FD and several variables

Univariate and multivariate analysis were used to study associations between FD and several anamnesis/initial reaction variables. Results are shown in further detail in Table 2.

Oxaliplatin-reactive patients

Seventy-four oxaliplatin-reactive patients were assessed during the 3-year period of the study. Characteristics of these specific patients and results of their diagnostic protocol are shown in Table 5. Additional data on ST and oxaliplatin-specific IgE statistical assessment as diagnostic tools are shown in Table 6.

Discussion

Highlighted results we find interesting for the reader

This is the first reported study in which more than 100 patients undergo DPT with antineoplastic and biological agents. Sixty-four percent (67/104) of all DPTs were negative. Hypersensitivity was excluded in 36% (67/186) of all referred patients (avoiding therefore the need for desensitization, and allowing them to normally continue with their treatments).

First time likelihood ratios along with sensitivity, specificity, PPV, and NPV are reported for oxaliplatin-specific IgE and ST in oxaliplatin-reactive patients who have undergone DPT to confirm or exclude hypersensitivity.

DPT: previous experience as diagnostic tool

In a recent publication by our group (13), we found that 21% of all referred patients showed a negative DPT with antineoplastic and biological agents. Moreover, DPT has been safely used as cornerstone in diagnostic protocols for hypersensitivity to several drugs such as nonsteroidal anti-inflammatory drugs (NSAID), betalactam antibiotics, antibiotics other than betalactams, and proton pump inhibitors (21–25). A recent article evaluating patients with unequivocal history of urticaria and/or angioedema after NSAID intake, in which all patients underwent DPT, showed that 21% (16/75) of patients did not react to any culprit-drug (25). Betalactam antibiotics data vary depending on populations and type of reaction; nevertheless, many patients with clear history of HSRs to these drugs show negative DPTs (22, 26, 27).

DPT prior to desensitization

Drug provocation test had never been used as a diagnostic tool prior to desensitization to antineoplastic and biological agents in previous works (7–11). Nevertheless, recent reports by our group with small samples of patients show that DPT prior to desensitization may be necessary and even optimal for several drugs (13–17), and other authors have used DPT even in patients with severe reactions (28). In our population, 32% of platins, 40% of taxanes, and 30% of biological agents showed a negative DPT; therefore, we believe protocols including DPT prior to desensitization may reduce the amount of patients who finally undergo desensitization. Data on DPT should be clearly stated in articles studying desensitization procedures, because omitting DPT prior to desensitization may lead to important selection bias (e.g., a high percentage of nonhypersensitive patients may undergo desensitization, and therefore, efficacy/effectiveness and safety could be overestimated).

Table 5 Characteristics and final diagnosis after completing the diagnostic protocol (anamnesis, skin testing (ST), oxalipatin-specific IgE, tryptase, drug provocation test) in 74 oxalipatin-reactive patients referred to our Desensitization Program during a 3-year period

#	Age	Sex	Grading initial HSR	Elapsed time (min)	Previous reactions	Previous exposures	RT	Skin testing	sigE (IU/l)	DPT	DPT Tryptase (ng/ml)	Initial symptoms					Final diagnosis (FD)
												C	G	R	CV	N	F
1	58	M	2	60	+	24	+	-	0.93	+	5.20	-	-	-	-	+	+
2	54	M	1	20	-	16	+	-	0.04	-	-	+	-	-	-	-	-
3	73	F	1	30	-	9	-	-	0.03	-	-	+	-	-	-	-	-
4	71	M	1	60	-	13	+	-	0.01	+	8.02	+	-	-	-	-	+
5	79	F	1	1440	-	0	-	-	0.01	-	-	+	-	-	-	-	-
6	71	F	1	10	-	23	-	5 ID	0	-	-	+	-	-	-	-	-
7	65	M	1	30	-	0	-	-	0	-	-	+	-	-	-	-	-
8	66	F	2	60	-	28	-	-	0	+	4.77	-	-	-	-	+	+
9	57	F	2	120	+	21	+	-	0.13	+	4.85	-	-	-	+	+	+
10	57	F	3	30	+	23	+	-	0	+	8.10	-	-	-	+	+	+
11	59	M	2	10	-	8	-	-	0.27	-	-	+	-	-	+	-	-
12	57	M	2	120	+	2	-	-	0.05	+	5.20	-	-	+	+	-	+
13	64	F	2	30	-	15	+	-	0.26	-	-	+	-	-	+	-	-
14	71	M	2	180	+	29	+	-	0.02	-	-	-	-	-	-	+	-
15	66	F	2	40	+	19	+	-	0.08	-	-	+	+	+	-	-	-
16	59	M	1	30	-	12	+	-	0.76	-	-	+	-	-	-	-	-
17	73	M	1	30	-	6	-	5 ID	0.32	-	-	+	-	-	-	-	-
18	76	M	1	240	-	7	-	-	0	-	-	+	-	-	-	+	-
19	62	F	2	120	-	0	-	-	0	-	-	-	+	+	+	-	-
20	52	M	2	60	-	11	-	-	0.05	-	-	+	-	+	+	-	-
21	62	F	2	60	-	12	+	-	0.44	-	-	+	-	-	+	+	-
22	50	M	1	60	-	25	+	-	0.03	-	-	-	-	-	-	+	-
23	64	M	1	60	-	14	+	-	0.01	-	-	-	-	-	-	+	-
24	71	F	2	90	-	0	-	-	0.09	-	-	-	-	+	-	-	-
25	69	M	1	40	-	6	-	-	0.01	+	4.77	+	-	-	-	-	+
26	55	M	2	30	-	8	-	-	0.09	+	6.07	+	-	+	+	-	+
27	66	F	2	30	+	8	-	-	0.03	+	3.70	+	-	-	+	-	+
28	63	F	2	30	-	3	-	-	0.01	+	2.25	+	+	-	-	-	+
29	48	M	1	90	+	5	-	-	0.06	+	1.23	+	-	-	-	-	+
30	80	M	1	60	-	15	-	-	0.03	-	-	+	-	-	-	-	-
31	42	M	3	5	-	8	-	-	0.05	-	-	+	-	+	-	-	-
32	63	F	1	120	+	10	-	-	0	+	39.6	-	-	-	-	+	+
33	77	M	2	120	-	1	-	-	0.02	-	-	-	-	+	-	-	-
34	52	F	1	90	+	14	+	-	0.38	-	-	-	-	-	-	+	-
35	50	M	1	10	+	7	-	5 SPT	0.72	NU	-	-	-	-	-	-	+
36	84	M	3	60	-	9	+	0.5 ID	0.05	NU	-	+	-	+	-	-	+
37	72	M	3	10	+	3	-	0.5 SPT	10.1	NU	-	+	+	+	+	+	+
38	58	M	2	15	+	7	-	5 SPT	0.21	NU	-	+	+	+	-	-	+
39	63	M	1	60	-	4	-	0.5 ID	0.33	NU	-	+	-	-	-	-	+

Table 5 (continued)

#	Age	Sex	Grading initial HSR	Elapsed time (min)	Previous reactions	Previous exposures	RT	Skin testing	sigE (IU/l)	DPT	DPT Tryptase (ng/ml)	Initial symptoms					Final diagnosis (FD)
												C	G	R	CV	N	F
40	75	F	2	60	+	3	-	0.5 ID	0.02	NU		+	-	+	-	-	+
41	76	M	2	30	-	8	-	0.5 ID	0.36	NU		+	+	-	+	-	+
42	52	F	2	10	-	7	-	0.5 ID	0.4	NU		+	+	+	-	-	+
43	64	F	3	10	-	9	+	5 SPT	1.21	NU		+	+	+	+	-	+
44	64	M	1	10	+	26	+	5 ID	0.71	NU		+	-	-	-	-	+
45	65	M	2	10	-	5	-	0.5 SPT	2.28	NU		+	+	+	+	-	+
46	51	M	1	30	+	10	-	0.5 ID	0.03	NU		+	-	-	-	-	+
47	73	M	3	31	-	7	-	5 SPT	0.21	NU		+	+	+	+	+	+
48	76	F	3	20	-	14	-	5 SPT	4.6	NU		+	+	+	+	-	+
49	51	M	1	90	-	12	-	5 ID	0.26	NU		-	-	-	-	-	+
50	72	M	2	10	-	10	+	0.5 SPT	0.07	NU		+	+	+	-	-	+
51	50	M	2	120	-	0	-	-	0.03	NU		+	+	-	+	-	UC
52	74	M	2	120	-	12	+	-	0.05	NU		+	-	-	+	-	UC
53	80	F	3	100	-	1	-	NU	2.02	NU		+	-	+	-	-	UC
54	77	M	2	120	-	1	-	-	0.10	-		-	-	+	-	-	-
55	74	F	3	135	+	1	-	NU	0.89	NU		-	+	+	+	+	UC
56	81	F	2	30	-	5	-	NU	0.84	NU		+	+	+	+	-	UC
57	74	M	1	30	+	5	-	NU	0.22	NU		+	-	-	-	-	UC
58	57	F	3	120	-	13	-	-	0.04	+	16.8	+	+	-	+	+	+
59	63	M	3	10	-	19	-	-	0.05	+	5.84	+	-	+	+	-	+
60	55	M	1	20	+	9	+	-	0.08	+	2.05	+	-	-	-	+	+
61	48	M	2	5	-	12	+	5 SPT	0.32	NU		+	+	+	+	-	+
62	51	M	2	5	-	1	+	5 SPT	0.10	NU		+	+	-	-	-	+
63	51	F	2	60	-	4	+	-	0.09	NU		-	+	+	+	-	UC
64	33	M	2	10	-	4	-	-	0.03	NU		+	+	-	+	+	UC
65	62	M	3	45	-	7	-	5 SPT	4.88	NU		+	-	+	-	-	+
66	44	M	3	30	-	5	+	5 ID	0.07	NU		+	+	+	+	-	+
67	72	F	3	60	+	8	+	5 ID	0.36	NU		+	-	+	-	-	+
68	59	F	1	60	-	0	-	-	0.06	NU		+	-	-	-	-	UC
69	67	F	3	120	-	1	+	-	0	NU		-	-	+	-	-	UC
70	56	M	1	10	-	12	-	0.5 ID	0.81	NU		+	-	-	-	-	+
71	63	F	2	30	-	2	-	-	0.04	+	7.94	+	+	-	-	-	+
72	52	M	1	30	+	6	-	-	0.27	-	-	+	-	-	-	-	-
73	49	F	3	10	-	11	-	0.5 ID	10.1	NU		+	+	+	+	+	+
74	48	M	1	90	+	4	-	-	0.03	+	2.27	+	-	-	-	-	+

RT, Retreatment; sigE, specific IgE; HSR, hypersensitivity reaction; DPT, drug provocation test; C, cutaneous; R, respiratory; G, gastrointestinal; CV, cardiovascular; N, neuromuscular; F, fever/chills; SPT, skin prick test; ID, intradermal test; NU, not undergone; UC, unconfirmed final diagnosis. Tryptase in positive DPTs was obtained 60 min after reaction. Positive converters: Patient 15 and patient 21 presented with a HSR during follow-up after a negative DPT (after 2 and 3 uneventful administrations, respectively). Number 15 converted to a positive SPT 0.5 and sigE of 4.5. Number 21 converted to a positive ID 0.5 and sigE of 2.28 IU/l.

Table 6 Assessing oxaliplatin-specific IgE and skin tests (prick test and intradermal test) as diagnostic tools in 74 oxaliplatin-reactive patients who included drug provocation test (DPT) in their diagnostic protocol

Oxaliplatin-specific IgE	Cutoff 0.10 UI/l (95% CI)	Cutoff 0.35 UI/l (95% CI)
Sensitivity	51% (37–65)	34% (29.9–47.1)
Specificity	71.9% (56.3–87.5)	90.3% (79.7–100)
PPV	73.5% (58.7–88.4)	85% (69.4–100)
NPV	48.9% (34.6–63.2)	45.9% (33.4–58.4)
Likelihood ratio +	1.8 (1.0–3.4)	3.5 (1.1–11.0)
Likelihood ratio –	0.7 (0.5–1.0)	0.7 (0.6–0.9)
ST (Prick and ID)	(95% CI)	
Sensitivity	57.5% (42.2–72.8)	
Specificity	91.7% (80.6–102.7)	
PPV	92% (81.4–102.6)	
NPV	56.4% (40.8–72.0)	
Likelihood ratio +	6.9 (1.8–26.7)	
Likelihood ratio –	0.4 (0.3–0.7)	

We calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratios for oxaliplatin-specific IgE (cutoff points in 0.10 and 0.35 UI/l), using final diagnosis (FD) as gold standard for the assessment. To avoid possible bias, DPTs were undergone regardless of oxaliplatin-specific IgE results.

Patients with 'unconfirmed' FD (patients who did not meet criteria to be considered either 'positive' or 'negative') were excluded. Of the total 74 oxaliplatin-reactive patients, 10 patients were excluded because they could not meet criteria to be considered either positive or negative in their FD.

DPT: safety and management

Even if mild reactions were found in 49% of DPTs and no deaths were reported, up to 11% of DPTs showed a severe reaction. DPT is a high-risk procedure to be performed in specialized centers equipped with specific resources, expert personnel, and a special area for these techniques (1, 13–17). Appropriate patient selection for DPT (by risk assessment, ST, and, in the near future, specific IgE) and management by drug-allergy experts are key-points to avoid unnecessary risks. Even if efforts have been made to find risk factors that may predict a severe reaction (29), DPT outcomes remain unpredictable in each individual patient.

No international guidelines for DPT with antineoplastic and biological agents have been published, so protocols could vary locally. Our DPT protocol is based on direct readministration of the culprit-drug under standard conditions (to avoid possible induction of tolerance due to lower infusion rates or intensified premedications).

In our population, 35 of the 37 DPT-reactive patients tolerated our 'restart protocol' with no additional reactions. Thus, whenever facing a positive DPT with antineoplastic or biological agents, cautiously restarting the culprit-drug infusion immediately after symptoms are controlled may be a

helpful approach to ensure reactive patients receive the desired antineoplastic or biological agent regardless of the DPT outcome. Previous studies with paclitaxel (30) and NSAID (28) have observed this phenomenon of culprit-drug tolerance within minutes–hours after a HSR with the culprit-drug.

To minimize risks, we believe the implementation of DPT protocols and 'restart protocols' should only be considered by expert allergists with clinical expertise in drug allergy and access to a multidisciplinary team approach to each individual patient, risk-management strategies, specialty-trained personnel, specific resources, and appropriate facilities (special areas for these techniques, such as MICU beds) (1, 3, 13).

Factors associated with a diagnosis

As in shown in Table 2, patients with history of previous reactions with the same culprit-drug showed an increased risk of a positive FD (RR, 3.99; 95% CI, 1.69–9.44). Many of these previous reactions are mild and not reported (14, 17, 31). Implementing measures to encourage early detection of mild reactions during antineoplastic or biological agents administration, and rapid referral to allergy specialists may prevent the risks of errors such as 'uncontrolled DPTs' (i.e., administering a culprit-drug to a reactive patient lacking allergy/risk assessment, in inappropriate environments, by untrained and/or unaware personnel).

All culprit-drugs showed a reduced risk of a positive FD when compared to platins. Interestingly, biological agents showed an increased risk (RR, 2.31; 95% CI, 1.21–9.83) of an unconfirmed FD, probably due to easy access to plenty therapeutic alternatives.

Cutaneous symptoms were associated with an increased risk of a positive FD (RR, 3.46; 95% CI, 1.41–8.47). In previous studies (13), over 90% of patients with a positive FD presented with these symptoms. Gastrointestinal symptoms (RR, 2.87; 95% CI, 1.69–16.07) were associated with an increased risk of a positive FD, and data are consistent with previous findings (18). Cardiovascular symptoms associated with an increased risk of unconfirmed FD (RR, 3.15; 95% CI, 1.79–12.28), and this could be explained by the fact that cardiovascular symptoms are found in severe reactions which may lead to avoiding DPT or to changing to alternative therapies. However, as we believe from our data and data from other groups (13–17, 25), symptoms or clinical history alone may not lead to a true diagnosis; this may be influenced by many factors, including other entities that may present with similar symptoms to anaphylaxis (20, 32).

On the other hand, some factors (gender, elapsed time, respiratory, neuromuscular, fever/chills, etc.) were not associated with FD. As opposed to common belief, we found initial reaction's severity was not associated with a positive FD (in our study population and under our diagnostic protocol). As we suspected from previous studies (13), we found no association between atopy or drug allergy and the FD. One study (33) found association between the risk of HSRs with carboplatin and reintroducing treatment after drug-free periods >12 months. We refer to this reintroduction as 'retreat-

ment', and we found no association between retreatment and FD in our population.

Oxaliplatin-reactive patients: ST, oxaliplatin-specific IgE, and possible phenotypes

Seventy-four oxaliplatin-reactive patients were referred and studied. Fifty-five percent (41/74) of them underwent DPT, and 59% (24/41) DPTs were negative. Thirty-three oxaliplatin-reactive patients did not undergo DPT, and the reasons for not undergoing DPT were as follows: 78% (26/33) did not consent to undergo DPT (after in-depth explanation of their individual risk–benefit assessment according to initial reaction and ST results), 15% (5/33) were classified as high-risk patients, and 6% (2/33) were changed to an alternative therapy.

All patients with negative DPT were followed: two of them became positive converters, as shown in Table 5. Oxaliplatin-reactive patients who become positive converters have been previously described (11). We believe oxaliplatin-reactive patients with negative DPT may benefit from close follow-up including screening ST. Similar preventive approaches have been previously proposed (34). Both of our positive converters underwent ST with a time interval >6 months after initial reaction; interestingly, other authors (35) have found association between positive conversion and these time intervals.

Several patients experienced fever/chills during their initial reactions with oxaliplatin (Table 5), but 'patient 32' (initial reaction consisting exclusively of fever/chills) presented with severe anaphylaxis during DPT, and patient's tryptase levels rose to 39.6 ng/ml. As it has been previously reported (14, 17), fever/chills during the administration of chemotherapy including oxaliplatin may be the prelude of more severe anaphylactic reactions during following administrations. Patients suffering these atypical symptoms (fever/chills) may also benefit from careful allergological assessment (17).

Both oxaliplatin-specific IgE and ST show good specificity, PPV, and positive likelihood ratio. This is especially true for oxaliplatin-specific IgE, as DPT was undergone regardless of the result of oxaliplatin-specific IgE. On the other hand, results for ST may be overestimated as many positive-ST patients did not consent DPT. In any case, sensitivity, NPV, and negative likelihood ratio for both tests seem surprisingly low, but are consistent with previous data (13). PPV and NPV are directly related to the prevalence of the studied disease/event; therefore, the results we show for PPV and NPV can only be applied to our population.

Additional findings: false-positive ST

Seven patients with positive ST (all of them positive intradermal tests) to paclitaxel 6 mg/ml, oxaliplatin 5 mg/ml, or carboplatin 10 mg/ml showed a negative DPT and no reactions during follow-up. Whether we are facing subclinical sensitiza-

tion, latent atopy, or irritant concentrations (9, 36) is yet to be established.

General limitations

There are some limitations to the study regarding conclusions for the groups of 'biological agents' and 'other drugs', namely the rather heterogenous study groups, the broad spectrum of drugs studied, as well as the most probably different mechanism involved.

Conclusions

- 1 These first reported data on DPT performed in more than 100 patients who have suffered HSRs to antineoplastic and biological agents make us conclude that implementation of DPT in diagnostic protocols is of vital importance when assessing these reactions, as hypersensitivity will be excluded in a considerable percentage of patients (36% of all referred patients, in our population) and therefore will reduce the risk of false-positive diagnosis of drug hypersensitivity based on 'suggestive' or 'unequivocal' clinical history.
- 2 Whenever used prior to desensitization, DPT is of vital importance for avoiding nonhypersensitive patients being subjected to desensitization (in our population, depending on culprit-drug, from 30% to 56% of patients referred after suffering a HSR showed a negative DPT and therefore could avoid desensitization).
- 3 We believe DPT is essential whenever more than one drug is involved in the reaction, when we need to validate diagnostic tools, and when we try to identify false-positive or false-negative results in diagnostic tools such as ST or specific IgE.
- 4 Even if 64% of all performed DPTs were negative, up to 11% of positive DPT showed a severe reaction: DPT is a risky technique and must be undergone by expert allergists in adequate facilities.
- 5 These first reported data on likelihood ratios, sensitivity, specificity, NPV, and PPV for ST and oxaliplatin-specific IgE (in oxaliplatin-reactive patients who have undergone DPT) make us conclude that, whenever positive, ST and oxaliplatin-specific IgE seem to be good tools to confirm oxaliplatin hypersensitivity. However, negative results seem less useful and require DPT, whenever feasible, to reach a diagnosis.

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Author contributions

All authors contributed to the design of the article, to the acquisition/analysis/interpretation of data, to draft the article, and to the final approval of the version to be published.

Conflicts of interest

There are no potential conflict of interests for any of the authors regarding this article. There are no financial interests, and there has been not any provision of study materials by their manufacturer for free or at a discount from current rates.

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