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Joana Queirós Gomes*, Liliana Patrícia Pereira Dias*, Patrícia Barreira, Joana Barradas Lopes, Maria João Sousa, Susana Cadinha, Daniela Malheiro

Relevance of the diagnosis of hypersensitivity reactions to antineoplastic and biological agents: experience with drug provocation test

Department of Allergy and Clinical Immunology, Centro Hospitalar Vila Nova Gaia/Espinho, Porto, Portugal
*The authors contributed equally to this work

Key words

Chemotherapy hypersensitivity reactions; drug provocation test; rapid desensitization; regular supervised administration; restart protocol.

Corresponding author
Liliana Patrícia Pereira Dias
Immunoallergology Service
Centro Hospitalar Vila Nova Gaia/Espinho
Rua Conceição Fernandes
4434-502 Vila Nova Gaia, Porto, Portugal
ORCID: 0000-0003-2285-4333
E-mail: liliana.pereira.dias@chvng.min-saude.pt

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Impact statement

This work highlights the safety and effectiveness of DPT in the assessment of HSRs to antineoplastics.

Summary

Background. *Evidence regarding drug provocation test (DPT) with chemotherapeutic agents is scarce. The aim of our study is to describe the experience of DPT in patients with a history of hypersensitivity reactions (HSRs) to antineoplastic and biological agents.* ***Methods.*** *Eight-year retrospective, observational, descriptive study of patients with a history of HSRs to chemotherapy who were submitted to DPT. Anamnesis, skin tests (ST) and DPT were analyzed. Patients with a negative DPT were submitted to at least one regular supervised administration (RSA). Patients with positive DPT or HSR during RSA were offered rapid drug desensitization (RDD).* ***Results.*** *A total of 54 patients were submitted to DPT. The most common suspected drugs were platins (n = 36), followed by taxanes (n = 11). Most of the initial reactions were classified as grade II (n = 39) according to Brown's grading system. ST with platinum (n = 35), taxanes (n = 10) and biological agents (n = 4) were negative, except for one intradermal test with paclitaxel, which was positive. A total of 64 DPTs were performed. Eleven percent of all DPTs were positive [platins (n = 6), doxorubicin (n = 1)]. Of the 57 RSA with the culprit drugs, 2 were positive (platins). The diagnosis of hypersensitivity was confirmed by DPT/RSA in 9 patients. All patients with positive DPT/RSA presented HSRs of equal or less severity than the initial one.* ***Conclusions.*** *DPT followed by RSA allowed to exclude HSRs in 45 patients (55 culprit drugs). DPT before desensitization prevents non-hypersensitivity patients from undergoing RDD. In our study DPT was safe, all reactions were managed by an allergist.*

Introduction

The diagnosis of neoplastic and inflammatory diseases has increased over the last years, leading to a larger number of patients exposed to antineoplastic and biological agents and to a rise in the incidence of hypersensitivity reactions (HSRs) (1-3).
These HSRs may be severe and life-threatening, jeopardizing first-choice treatments and leading to less effective and tolerated treatments which affect patient's survival and prognosis (4).
Rapid drug desensitization (RDD) is a cost-effective technique that enables hypersensitive patients to receive their first-choice treatments (5, 6). RDD temporarily modifies the patient's immune response to drug antigens, allowing the full dose to be achieved in a few hours without major side effects (5, 7-10).
In a recent study, it has been reported that a percentage of patients with suspected HSRs to antineoplastic and biologic agents may not be allergic and will not need RDD, making drug provocation testing important in de-labeling and economizing resources (1, 2).
Drug Provocation Test (DPT) is a diagnostic technique that involves administering a drug to a patient who carries a label of an unconfirmed allergy to that drug, and it is the gold standard to confirm or rule out an allergy (4, 11).

DPT is helpful to avoid unnecessary RDDs, to study patients who received more than one drug simultaneously and to find alternative drugs in hypersensitive patients (6).
Despite these invaluable benefits, DPT is a high-risk technique, especially when dealing with highly sensitizing intravenous drugs such as chemotherapy or biologics agents (1, 3, 4, 12). Therefore, careful patient selection and optimal risk-management plans are critical to ensure patient safety during intravenous DPT (11, 13, 14). Despite the European Academy of Allergy and Clinical Immunology (EAACI) international consensus recommendations on performing diagnostic DPTs (4), whenever feasible, prior to drug desensitization, the financial and staffing expenditure linked to the high-risk technique of DPT with chemotherapy can explain why real-life data are still scarce (6).
The aim of this study was to describe the experience of DPTs in patients with a history of HSRs to antineoplastic and biological agents in an Allergy Department of a Tertiary Hospital in Portugal.

Materials and methods

Study design and population

The authors performed a retrospective, observational, descriptive and inferential review of patients with a history of HSRs to antineoplastic and biological agents who were submitted to DPT, during an eight-year period (between 2014 and 2022) in our Allergy and Clinical Immunology Department. Patients were also required to be older than 18 years of age and able to provide written informed consent before each DPT.

Informed consent statement

This study was conducted in accordance with the ethical standards established in the Declaration of Helsinki of 1946 (15). The institutional ethics committee approved the study, and informed consents were signed by patients and allergists.

Initial reaction classification

Initial reactions were classified as immediate (occurring during drug infusion or within 1 hour after treatment) and non-immediate (> 1 hour after completion of the infusion). The latter were excluded. Immediate reactions were graded according to both the Brown's grading system (BGS) (grade I, II and III corresponding to mild, moderate and severe reactions, respectively) (16) and the Ramon y Cajal University Hospital (RCUH) classification (grade I-IV, corresponding to mild, moderate, severe and anaphylactic shock, respectively) (1, 17) (**table I**).

Table I *- Brown and RCUH classification for grading system for hypersensitivity reactions.*

Brown Classification (14)		
I. Mild Reaction	**II. Moderate reaction**	**III. Severe Reaction**
Skin and subcutaneous tissues only: • Generalized erythema • Urticaria • Periorbital edema • Angioedema	Features suggesting respiratory, cardiovascular, or gastrointestinal involvement: • Dyspnea, stridor, wheeze, chest or throat tightness. • Nausea, vomiting, abdominal pain • Dizziness (presyncope), diaphoresis	Hypoxia, hypotension, or neurologic compromise: • Cyanosis or $SpO_2 \leq 92\%$ at any stage • Hypotension (SBP < 90mmHg in adults) • Confusion, collapse, loss of consciousness or incontinence

RCUH classification (15)			
I. Mild Reaction	**II. Moderate reaction**	**III. Severe Reaction**	**IV. Anaphylactic shock**
• Erythema • Pruritus • Local urticaria/angioedema • Fever/chills (< 38 °C) • Mild back pain	Slow onset (> 15 min): • Generalized urticaria/angioedema • Coryzal symptoms • Irritative cough • Dyspnea ($SpO_2 > 92\%$) • Nausea • Abdominal pain • Severe back pain • Fever (> 38 °C)	Rapid onset (< 15 min): • Generalized urticaria/angioedema • Coryzal symptoms • Irritative cough And/or manifestation of: • Throat tightness with dysphagia and/or dysphonia and/or stridor • Wheezing • Chest tightness • Vomiting • $SpO_2 < 92\%$ • Diaphoresis • Dizziness • Hypertension	Immediate onset (or rapid progression) of any of the latter and manifestation of any of the following: • Hypotension • Cyanosis • Sense of impending doom • Faintness • Loss of sphincters control • Cardiovascular and/or respiratory arrest

Diagnostic protocol

Patients were evaluated by detailed clinical history: characterized according to demographic data, histological subtypes of cancer, staging, therapeutic cycle involved in HSR and severity of reaction. Patients were eligible for an allergic diagnostic work-up if the oncologist confirmed the absolute need to maintain the treatment. Patients were then classified in two groups depending on their risk assessment: favorable or non-favorable risk for DPT.

Risk-assessment outcomes included a combination of several factors, namely, patient-related factors (any reason for frailty or comorbidities that would lower the possibilities of anaphylaxis survival, as uncontrolled asthma or lung diseases with FEV1 < 70%, unavoidable use of beta-blocker drugs and mastocytosis), HSR-related factors (severity of the initial reaction) and endophenotyping (results of the allergy work-up such as skin testing (ST) or biomarkers such as tryptase and IL-6) (1, 14).

Whenever appropriate, ST, including skin prick testing (SPT) and intradermal testing (IDT), were performed according to concentrations and safety measures for cytostatic drugs by European Network on Drug Allergy of the EAACI (18).

Patients with negative or equivocal ST results, favorable risk assessment and who signed the informed consent (after an explanation of their individual risk–benefit assessment) were submitted to DPT.

DPTs were performed on patient's scheduled treatment, in which the desired full dose of the culprit drug was administered according to the manufacturer's instructions, respecting infusion rates of the standard regimes and with no additional premedication rather than the standards according to manufacturer/ institutional protocols (4, 13). Beta-blockers and ACE inhibitors were held prior to the procedure (2).

In order to keep standard regimens, any additional required medication, as other antineoplastics, were also administered after DPT following oncologist prescription. As appropriate, provocations with other drugs involved in the initial reaction were performed before DPT with the culprit drug (2, 4).

DPT was considered positive when it reproduced the original symptoms or showed an objective HSR. In the case of a positive DPT, the infusion was stopped and the HSRs were treated according to severity (1, 2, 4, 19). Whenever possible, once symptoms were controlled, the infusion was immediately restarted at an adjusted desensitization protocol until all the medication was administered ("restart protocol") (1, 2, 4, 12, 17).

Patients with a negative DPT were submitted to at least one regular supervised administration (RSA). RSA consists of drug administration at standard time, without additional premedication, under the supervision of an allergist in our Allergy/Oncology Day Care Unit (2).

Patients with negative DPT and RSA were considered non-allergic and continued with their regular chemotherapy sessions in the Oncology Unit.

Patients with positive ST, positive DPT, HSRs during RSA and/ or non-favorable risk assessment were offered RDD, for which we used a modified, 12 step-protocol, described by Castells *et al.* (8, 9, 20-22).

Trained personnel performed ST, DPT, RSA and RDD. ST were performed in our Allergy Day Care Unit and DPT, RSA and RDD in a special area of Allergy/Oncology Day Care Unit, with a 1:2 nurse-to-patient ratio, allergist at the bedside, hazardous drugs handling resources, all the necessary equipment to address severe anaphylaxis and rapid access to the intensive care unit.

Statistical analysis

Statistical analysis was performed using the software IBM SPSS Statistics for Windows, version 26. A descriptive statistical analysis was performed. For variables with normal distribution, we present mean and standard deviation, and for variables without normal distribution, median and interquartile range (IQR).

Results

Demographic and clinical characteristics

A total of 54 patients (34 female and 20 male) with suspected HSRs to chemotherapy agents were submitted to DPT during an eight-year period, from January 2014 to august 2022. The mean age of the study population at the time of the DPT was 62 ± 13 years (ranging from 19 to 83 years). The most common malignancies were colon, ovarian and breast adenocarcinoma, followed by lymphoma. Eight patients had more than one drug implicated in the initial reaction (6 patients had 2 and 2 patients had 3), bringing the total number of DPT to 64. Platins (n = 36) were the most common suspected drugs, followed by taxanes (n = 11), biological agents (n = 8) and others antineoplastic agents in 9 patients. A total of 24 patients (44% of the 54 patients) were under curative treatment. Patients' characteristics are summarized in **table II** and **table III**.

Characteristics of initial HSRs

Clinical manifestations and severity of the 54 suspected HSRs (total 64 culprit drugs) are illustrated in **figure 1**. All initial reactions were immediate. According to BGS (16) and RCUH classification (17), respectively, HSRs were characterized as grade I in 25% (n = 16) *vs* 15.6% (n = 10), grade II in 60.9% (n = 39) *vs* 59.5% (n = 38), grade III in 14.1% (n = 9) *vs* 25% (n = 16) and no patients were classified in grade IV according to RCUH. The most frequent clinical manifestations were cutaneous in 57.8% (n = 37) and respiratory in 48.4% (n = 31). In 54.7% (n = 35), the initial reaction was classified as anaphylaxis.

The median number of cycles until the first episode of HSR occurred was 3 cycles (minimum 1, maximum 20; IQR 7). The first episode of HSR to platins occurred at a median 8 cycles (minimum 1, maximum 20; IQR 7) and lower for other drugs:

Table II *- Patient characteristics.*

Patient	Gender	Age	Cancer	Suspected culprit drug	Skin Test	HSR cycle	Severity (Brown)	Severity RCUH)	Tryptase reaction	DPT	RSA	Positive DPT/RSA		Treatment session completed	RDD	Final diagnosis
												Brown	RCUH			
1	F	59	Colon	Oxaliplatin	-	3	II	III	3.00	-	-				N/A	-
2	F	69	Lymphatic	Cyclophosphamide	N/A	2	II	II		-	-				N/A	-
				Etoposide	N/A	2	II	II		-	-				N/A	-
				Bleomycin	N/A	2	II	II		-	-				N/A	-
3	F	72	Colon	Oxaliplatin	-	2	II	II		-	-				N/A	-
				Docetaxel	-	2	II	II		-	-				N/A	-
4	F	65	Colon	Bevacizumab	-	2	III	III		-	-				N/A	-
				Oxaliplatin	-	2	III	III		+	N/A	II	II	Yes	Yes	+
5	F	51	Ovarian	Paclitaxel	-	3	II	II		-	-				N/A	-
				Carboplatin	-	3	II	II		+	N/A	I	I	Yes	Yes	+
6	M	69	Colon	Oxaliplatin	-	1	II	II		-	-				N/A	-
				Cetuximab	-	3	II	II		-	-				N/A	-
7	F	19	Lymphatic	Bleomycin	N/A	1	I	II		-	-				N/A	-
				Doxorubicine	N/A	1	I	II	6.00	-	-				N/A	-
				Vimblastine	N/A	1	I	II	6.00	-	-				N/A	-
8	M	72	Parotid	Docetaxel	-	2	II	II		-	-				N/A	-
				Trastuzumab	N/A	2	II	II		-	-				N/A	-
9	F	68	Colon	Panitumumab	N/A	9	I	I	4.40	-	-				N/A	-
				Oxaliplatin	-	9	I	I	4.40	-	-				N/A	-
10	M	59	Colon	Oxaliplatin	-	11	II	III		-	-				N/A	-
11	F	52	Colon	Oxaliplatin	-	2	II	III		+	N/A	II	II	No	No[b]	+
12	M	66	Colon	Oxaliplatin	-	12	II	III		-	-				N/A	-
13	F	65	Colon	Irinotecan	N/A	7	I	I		-	-				N/A	-
14	M	73	Lung	Nivolumab	-	5	II	III		-	-				N/A	-
15	M	83	Stomach	Oxaliplatin	-	5	I	II		-	-				N/A	-
16	F	57	Endometrial	Paclitaxel	-	1	II	II		-	-				N/A	-
17	F	79	Colon	Oxaliplatin	-	1	II	II		-	-				N/A	-
18	F	74	Colon	Oxaliplatin	-	1	II	II		-	-				N/A	-
19	F	63	Colon	Oxaliplatin	-	9	II	II		-	-				N/A	-
20	M	61	Pancreas	Oxaliplatin	-	8	I	I		-	-				N/A	-
21	F	71	Ovarian	Carboplatin	-	14	II	II		-	+	II	II	Yes	Yes	+
22	M	60	Colon	Oxaliplatin	-	19	II	III		-	-				N/A	-

Patient	Gender	Age	Cancer	Suspected culprit drug	Skin Test	HSR cycle	Severity (Brown)	Severity RCUH)	Tryptase reaction	DPT	RSA	Positive DPT/RSA		Treatment session completed	RDD	Final diagnosis
												Brown	RCUH			
23	F	62	Breast	Paclitaxel	+[a]	1	I	I		-	-				N/A	-
24	F	57	Colon	Oxaliplatin	-	4	II	II		-	-				N/A	-
25	F	65	Ovarian	Carboplatin	-	19	II	II		-	-				N/A	-
26	M	45	Colon	Oxaliplatin	-	9	II	II		-	-				N/A	-
27	F	66	Breast	Docetaxel	-	1	III	III		-	-				N/A	-
28	M	74	Breast	Docetaxel	-	8	III	III	3.70	-	-				N/A	-
29	F	73	Breast	Docetaxel	N/A	1	I	I	4.00	-	-				N/A	-
30	F	73	Ovarian	Carboplatin	-	12	II	II		-	-				N/A	-
31	F	65	Colon	Oxaliplatin	-	7	III	III		-	-				N/A	-
32	M	47	Hematologic	Rituximab	N/A	2	I	II		-	-				N/A	-
33	M	52	Colon	Oxaliplatin	-	7	II	II	8.70	-	+	I	I	Yes	Yes	+
34	F	55	Stomach	Oxaliplatin	-	1	II	II		-	-				N/A	-
35	F	48	Stomach	Oxaliplatin	-	3	II	II		-	-				N/A	-
36	M	70	Hematologic	Rituximab	N/A	1	II	II		-	-				N/A	-
37	M	60	Colon	Oxaliplatin	-	8	II	II		-	-				N/A	-
38	F	32	Colon	Oxaliplatin	-	12	II	II		+	N/A	I	I	Yes	Yes	+
39	F	60	Breast	Paclitaxel	-	18	II	III		-	-				N/A	-
40	F	46	Stomach	Cisplatin	-	1	II	II		-	-				N/A	-
41	M	69	Lung	Nivolumab	-	2	III	III		-	-				N/A	-
42	F	62	Colon	Oxaliplatin	-	1	II	II		-	-				N/A	-
43	F	79	Ovarian	Placlitaxel	-	8	III	III		-	-				N/A	-
44	F	50	Pancreas	Oxaliplatin	-	8	II	II		-	-				N/A	-
45	F	57	Colon	Oxaliplatin	-	1	II	II		-	-				N/A	-
46	M	29	Skin	Doxorubicine	N/A	3	II	II		+	N/A	I	I	Yes	Yes	+
47	M	62	Colon	Oxaliplatin	-	10	I	I		-	-				N/A	-
48	F	72	Pancreas	Irinotecan	N/A	3	I	II		-	-				N/A	-
49	M	76	Colon	Oxaliplatina	-	20	I	I		-	-				N/A	-
50	F	81	Ovarian	Carboplatin	-	9	III	III		+	N/A	II	II	Yes	Yes	+
51	M	73	Colon	Oxaliplatin	-	18	II	II		-	-				N/A	-
52	F	55	Endometrial	Carboplatin	-	14	III	III	9.90	+	N/A	II	II	Yes	Yes	+
53	M	54	Ovarian	Carboplatin	-	15	I	I		-	-				N/A	-
54	F	63	Endometrial	Paclitaxel	-	2	II	II		-	-				N/A	-

DPT: drug provocation test; HSR: hypersensitivity reactions; ID: intradermal tests; N/A: not applicable; RDD: rapid drug desensitization; RCUH: Ramon y Cajal University Hospital classification; RSA: regular supervised administration; [a]positive ID at 10^{-1} (0.1mg/ml); [b]treatment was changed by patient oncologist due to oncologic disease progression.

Table III *- Characteristics of the patients referred to our department that were submitted to a Drug Provocation Testing.*

Characteristics	Number of patients, n(%)
Primary diagnosis	
Colorectal adenocarcinoma	24 (44.4%)
Breast adenocarcinoma	5 (9.3%)
Serous ovarian	5 (9.3%)
Endometrial	
Endometrioid	2 (3.7%)
Clear cell	1 (1.9%)
Serous	2 (3.7%)
Stomach adenocarcinoma	4 (7.4%)
Pancreatic adenocarcinoma	3 (5.6%)
Squamous cell lung	2 (3.7%)
Chronic lymphocytic leukemia	2 (3.7%)
Non-Hodgkin lymphoma	2 (3.7%)
Parotid adenocarcinoma	1 (1.9%)
Kaposi Sarcoma	1 (1.9%)
Treatment	
Curative	24 (44.1%)
Paliative	30 (55.6%)
History of atopy	5 (9.3%)
Culprit-drug	**Number of culprit-drugs, n (%)**
Platins	36 (56.3%)
Oxaliplatin	28 (43.8%)
Carboplatin	7 (10.9%)
Cisplatin	1 (1.6%)
Taxanes	11 (17.2%)
Paclitaxel	6 (9.4%)
Docetaxel	5 (7.8%)
Biological agents	8 (12.5%)
Rituximab	2 (3.1%)
Nivolumab	2 (3.1%)
Cetuximab	1 (1.6%)
Bevacizumab	1 (1.6%)
Panitumumab	1 (1.6%)
Transtuzumab	1 (1.6%)
Other drugs	9 (14.1%)
Liposomal Doxorubicine	2 (3.1%)
Irinotecan	2 (3.1%)
Bleomycin	2 (3.1%)
Etoposid	1 (1.6%)
Cyclophosphamide	1 (1.6%)
Vinblastine	1 (1.6%)

2 (1,18; IQR7) for taxanes and 2 (1, 9; IQR3) for biologics. Thirty-nine percent (25 out of 64) of the HSRs occurred after the sixth cycle.

Skin tests

SPT and IDT were performed with 50 culprit drugs, platinum compounds in 36 patients, taxanes in 10 and biological agents in 4. All tests were negative, except one positive IDT with paclitaxel 0.1 mg/ml. Interestingly, the patient with the positive ST had a negative DPT/RSA and experienced no reactions in the following cycles.

Drug Provocation Test outcomes

Results are shown in further detail in **figure 2** and **table IV**.

A total of 64 DPTs were performed with the culprit drug: 89.1% (n = 57) were negative and 10.9% (n = 7) were positive, all mild or moderate reactions according to BGS and RCUH classification. No patient had a positive DPT to more than one drug.

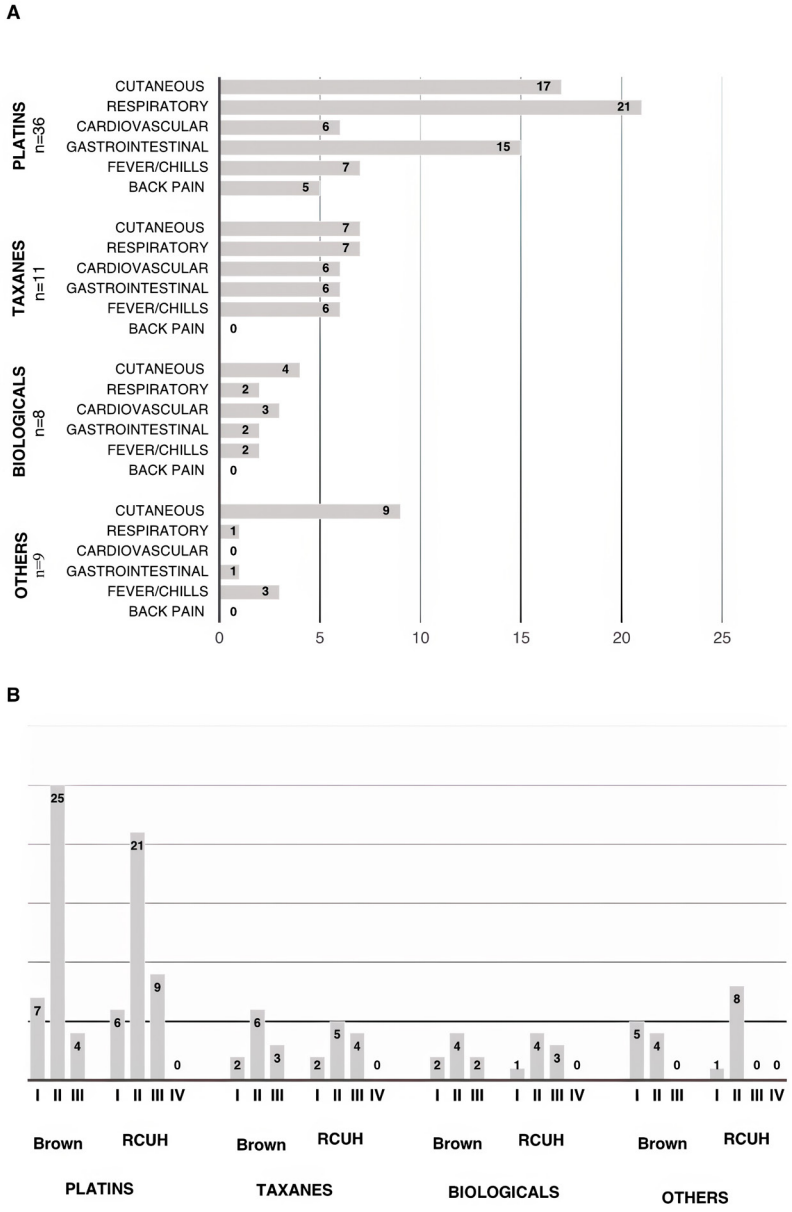
Six of these 7 patients (85.7%) had a positive DPT with platins: 3 patients with oxaliplatin and the other 3 with carboplatin. In patients with HSR to oxaliplatin, the reactions were: facial erythema, nausea and back pain; nausea and chills (T < 38 °C); local urticaria on the abdomen. In patients with HSR to carboplatin: facial erythema and pruritus; palmoplantar pruritus and nausea in two patients. One patient had a positive DPT with doxorubicin: erythema and itching on the abdomen and legs. All of them were treated with intravenous clemastine and intravenous methylprednisolone. All patients with positive DPT to carboplatin had a previous chemotherapy cycle and the median time interval between the HSR and previous chemotherapy cycle was 16.7 months (minimum 4 months, maximum 36 months).

Patients with a negative DPT were submitted to at least one RSA. Two of the 57 patients with a negative DPT (3.5%), suffered a reaction with platins during RSA: one patient with oxaliplatin [generalized erythema and chills (T < 38 °C)] and other with carboplatin (facial erythema, irritative cough and abdominal pain). These patients were treated with intravenous clemastine, methylprednisolone and inhaled beta 2 agonists in those with respiratory symptoms.

All DPT/RSA-reactive patients presented HSRs of equal or less severity than the initial one and 8 out of the 9 DPT/RSA-reactive patients tolerated a full dose of the culprit drug on the same day of the DPT/RSA ("restart protocol").

RDD was performed in 8 of the 9 (88.9%) patients with confirmed HSRs (positive DPT or RSA with the respective drug involved in the HSR). All patients completed the proposed chemotherapy desensitization protocol. One patient (RSA positive to carboplatin) discontinued treatment, due to progression of the oncological disease, so he did not undergo desensitization.

Figure 1 - (A) *Clinical manifestations of the 54 suspected HSRs with chemotherapeutic agents (total 64 culprit-drugs) referred during an eight-year period for DPTs;* ***(B)*** *Severity of HSRs according BGS and RCUH classification.*

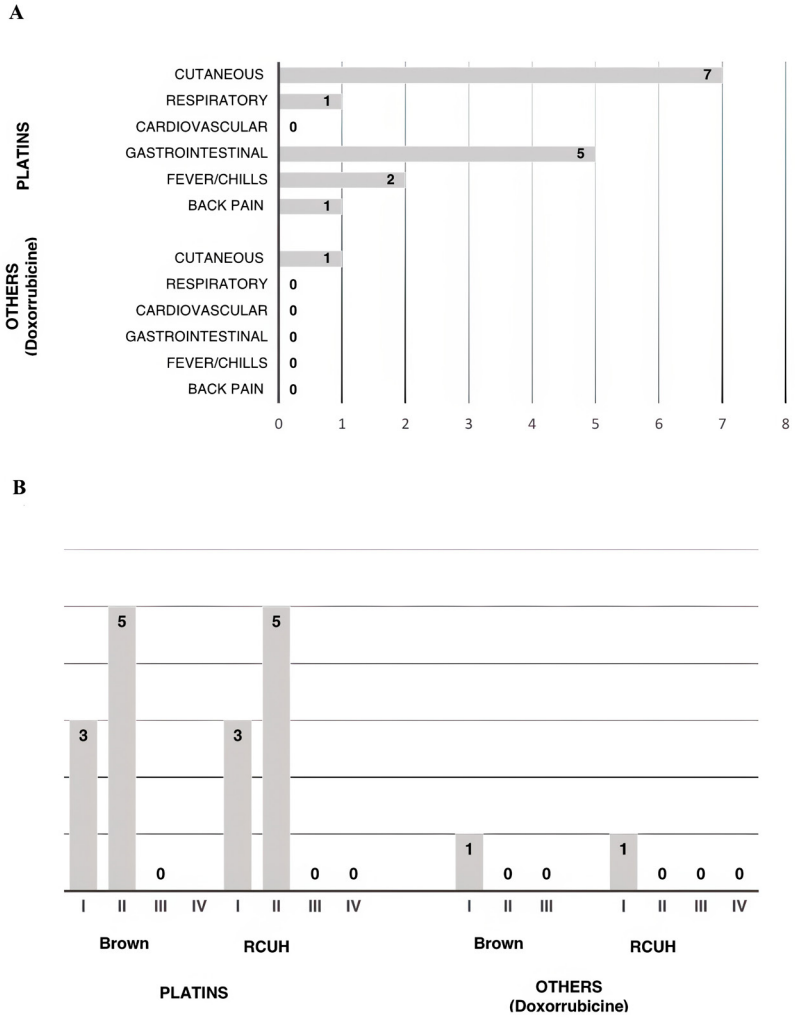


Discussion and conclusions

DPT is a gold standard diagnostic technique used in the study of drugs HSRs (23). More recently, the application of DPT has extended to address chemotherapy and monoclonal antibodies (1, 2). As with other drugs, the diagnostic assessment of HSRs to chemotherapeutics is essential. For patients with malignancies, changing to a second line agent after a HSR may negatively impact quality of life and life expectancy (3, 12).

In this study we report our experience with DPTs with antineoplastic and biological agents. We performed 64 DPTs with platinum compounds, taxanes, biological agents and others antineoplastic agents, in 54 patients who experienced immediate HSRs. Eighty-nine percent (57/64) of DPTs were negative. All

Figure 2 - (A) *Clinical features of HSR in the DPT (n = 7) and RSA (n = 2) of the 9 patients;* ***(B)*** *Severity of HSRs in the DPT and RSA according BGS and RCUH classification.*



patients with negative DPTs were followed during subsequent standard drug administration (RSA), which was positive in 2 (3.5%) patients (carboplatin and oxaliplatin). This approach (DPT/ RSA) allowed the exclusion of hypersensitivity in 85.9% (55/64) of the suspected culprit drugs, de-labeling 83.3% (45/54) of patients. If we had not performed DPT or RSA, this would have caused an unnecessary estimate increase of 85.9% in RDDs. This approach avoided the need for desensitization or switching to second-line therapy and allowing them to normally continue their treatment (6). It is important to emphasize the role of the RSA, if it was not performed with allergology surveillance, we would have misdiagnosed 2 patients.

In our population, 8 out of the 9 patients with positive DPT/ RSA achieved a full dose of the culprit drug on the same day of the DPT/RSA (1, 2, 14, 17, 24). Once symptoms were stabilized and the patient was asymptomatic, the infusion was restarted with 1 bag desensitization protocol (1/1,000 of the original infusion, 2-fold dose increments, along with increasing infusion rate each 15 minutes until the remaining medication was administered) – "restart protocol".

Patients with negative study (DPT and RSA) had no further reactions after follow-up with their oncologists.

In our study 8 patients had more than one culprit drug implicated in reaction (2 patients had 3 drugs and 6 patients had 2). DPT seems to be a safe and cost-effective technique to establish diagnosis in patients who received more than one drug simultaneously (1, 6, 25).

In our sample, most patients were undergoing palliative care, which requires treatment maintenance for long periods (26-28).

Table IV - *Outcomes of 64 DPT and 57 RSA with antineoplastic agents in 54 patients.*

	Positive, n(%)	Negative, n(%)	Total, n(%)
DPT (n = 64)	7 (10.9%)	57 (89.1%)	64 (100%)
Platins (n = 36)	6 (9.4%)	30 (46.9%)	36 (56.3%)
Taxanes (n = 11)	0	11 (17.2%)	11 (17.2%)
Biological (n = 8)	0	8 (12.5%)	8 (12.5%)
Other (n = 9)	1 (1.6%)	8 (12.5%)	9 (14.1%)
RSA (n = 57)	2 (3.5%)	55 (96.5%)	57 (100%)
Platins (n = 30)	2 (3.5%)	28 (49.1%)	30 (52.6%)
Taxanes (n = 11)	0	11 (19.3%)	11 (19.3%)
Biological (n = 8)	0	8 (14%)	8 (14%)
Other (n = 8)	0	8 (14%)	8 (14%)

Forty-four percent (24/54) were undergoing curative treatment, with a high percentage of recurrence described in some neoplasms. A percentage of these patients may be submitted again to the initial treatment scheme; therefore, it is important to confirm or exclude hypersensitivity to antineoplastic agents (26-28).

Prior to DPT, appropriate selection of patients should be carried out, assessing risk by severity scales (BGS and RCUH classification) and ST (1, 16-18). SPT and IDT performed to detect drug specific IgE are only useful for some chemotherapeutic drugs (6). Platinum ST are recommended and validated (8, 29). In our study, despite all 35 patients had negative STs for platinum salts, 8 of those patients had positive DPT/RSA, 4 with oxaliplatin (3 positive DPTs and 1 reaction during the RSA) and 4 patients with carboplatin (3 DPTs and 1 RSA). STs with paclitaxel and docetaxel predictive value has not yet been demonstrated, although some authors recommend its use in the allergological workup (30, 31). In our study, ST for taxanes were negative in 90% (9/10) of the patients. One patient presented positive IDT with paclitaxel in 10^{-1} concentration (0.1 mg/ml). In this case, the suspected HSR was mild (grade I), so the DPT followed by RSA were performed with no reactions experienced.

DPTs is a high-risk procedure that should be performed in specialized centers equipped with specific resources and expert professionals (1, 3, 4, 12). When DPT is performed under these conditions it has a good safety profile (2, 23, 32).

In our population, all patients with positive DPT/RSA presented HSRs of equal or less severity than the initial one. Mild reactions were found in 44.4% and moderate reactions in 55.6% of DPTs/RSA and no severe reactions or deaths were reported. In the group of patients with positive DPT/RSA, all reactions were managed by an allergist and no patient needed medical emergency activation or intensive care hospitalization.

Our results are in accordance with other studies published in the last years, namely in the RCUH studies, 64% (2) and 67% (1) of all performed DPTs were negative, and only 11% (2) and 15% (1) of all performed DPTs showed a severe reaction, according to Brown's classification (16).

General limitations

Our study has a number of limitations, as it is a single-center study, with a wide spectrum of drugs studied (platins, taxanes, biologics and other chemotherapeutic agents), and the groups of patients labeled as allergic are very heterogeneous. Further investigations with different populations, standardization of DPTs protocols and selection of candidates are needed.

Tryptase and IL-6 levels were not measured in all initial reactions, and the lack of these data can lead to an incorrect interpretation of some reactions.

In conclusion, our study demonstrated the safety and effectiveness of DPTs in the assessment of immediate reactions to chemotherapeutic drugs. In our sample, DPT followed by RSA allowed us to exclude HSRs in 45 patients (55 culprit drugs). Without RSA we would have missed the diagnosis in 2 patients, who could have had a potentially more severe reaction without the support of the allergy specialist.

All DPT/RSA-reactive patients presented HSRs of equal or less severity than the initial one, there were no severe reactions and only one did not complete the full dose.

DPT before desensitization prevents non-hypersensitivity patients from undergoing unnecessary desensitization. Our approach (DPT followed by RSA) enabled de-labeling of 83.3% of patients with suspected HSR to one or more chemotherapy agents, corresponding to a total of 85.9% suspected drugs that were excluded and, therefore, desensitization was avoided.

Access to a multidisciplinary team led by experts in drug allergy was very helpful to the optimal management of these patients.

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Contributions

JQG, LPPD: conceptualization, investigation, formal analysis, writing - original draft. PB, JBL, MJS, SC, DM: writing - review & editing. DM: resources.

Conflict of interests

The authors declare that they have no conflict of interests.

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