ORIGINAL ARTICLE

A single center experience in the management of suspected hypersensitivity reactions to chemotherapy

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Summary

Background. Hypersensitivity reactions to chemotherapy are increasing, thus there is a need to implement a correct diagnostic pathway to avoid switch to second line therapies or unnecessary drug desensitization. The objective of the study was to evaluate our experience in the management of immediate reactions to chemotherapy, focusing on the role of drug provocation test. **Methods.** Observational longitudinal study, where the allergological work-up included: patient's clinical history, characteristics of the reaction comprehensive of its phenotype ("type 1", "CRR", "either", "mixed"), skin testing (ST) and drug provocation test (DPT), when the risk assessment was favorable. The work-up was considered positive if ST or DPT resulted positive. **Results.** 162 patients were enrolled and most of them were delabled (98/162, 60.5%). The probability of delabeling was higher when the reaction involved taxanes ($p<0.005$), occured during the first drug exposure ($p<0.05$) and presented with "CRR" phenotype ($p<0.005$). The work-up was considered positive in 53 patients (32.7%) and they were mainly patients who reinitiated treatment after a gap ($p=0.001$) and experienced "type 1" reactions ($p<0.05$). **Conclusions.** The thorough evaluation has allowed us to identify different subsets of patients requiring different managing approaches. Furthermore, we confirmed the need and safety of implementing drug provocation test.

Impact statement

This paper provides a thorough characterization of a large cohort of patients experiencing suspected hypersensitivity reactions to chemotherapy and a safe and practicle algorithm on how to manage them.

KEY WORDS

Chemotherapy; hypersensitivity reactions; drug provocation test; phenotype; delabeling.

INTRODUCTION

Antineoplastic drugs are widely used in clinical practice and still represent the gold standard for the treatment of many cancer types, alone or in combination with targeted therapies. Chemotherapy (CHT) infusions, however, can be complicated by hypersensitivity reactions (HSRs) (1). These can have serious consequences, ranging from fatal events to drug discontinuation and switch to second-line treatments with worsening of the prognosis (2).

Drug desensitisation (DD) represents the cornerstone in the management of these patients, as it enables the continuation of first-line treatments despite HSRs (3). DD procedures, however, are time consuming (5-6 hours), resource-intensive and require highly specialized personnel. Furthermore, the tolerance induced by DDs is only temporary, meaning that the DD must be repeated at each drug administration (4). Therefore, these procedures should only be performed in highly selected patients with a confirmed drug hypersensitivity, after an extensive allergological work-up.

At present, the management of HSRs to CHT is based on detailed clinical history, risk stratification, skin testing (ST) and Drug Provocation Test (DPT) (5). DPT consists in the controlled administration of the culprit drug and despite being a high-risk procedure, it has shown a good safety profile when performed in patients with a favorable risk assessment (6-8). It is used to confirm or rule out hypersensitivity (2,9), though data on its use for CHT is limited to few highly specialized Centers (9-11). The diagnosis is further complicated by the lack of reliable *in vitro* tests, as the evidence regarding the use of basophil activation test is still scarce (11-13), and by the limited knowledge regarding acute phase biomarkers (14,15).

The main objective of this study was to evaluate the experience of our Centre with a clinical-laboratory diagnostic algorithm, comprehensive of DPT, as a safe delabeling tool in the management of HSRs to CHT.

METHODS

Study design and phenotyping of reactions

We conducted an observational longitudinal study of a cohort of patients who experienced an immediate (<1 hour) reactions to CHT, consecutively referred to the Immunoallergology Unit at Careggi University Hospital in Florence from December 2020 to October 2024. The diagnostic procedures were performed according to current standard clinical practice and a written informed consent was obtained from recruited patients.

All patients underwent an initial assessment comprehensive of complete medical history and evaluation of the clinical characteristics of the reactions. As proposed by *Silver et al* (16), the reaction phenotypes were defined according to their symptoms in: "type 1" (pruritus, urticaria, angioedema, nasal congestion, sneezing, wheezing, cough, throat tightness, tongue swelling), cytokine release reactions "CRR" (fever, chills, chest pain, backpain, headache, other pain), "mixed" (involving both type 1 and CRR symptoms) and "either" (flushing, warmth, erythema, dyspnea, oxygen desaturation, chest tightness, tachycardia, presyncope, syncope, hypo- or hypertention, nausea, vomiting, abdominal pain, diarrhea, bloating, reflux, numbness, weakness, seizures, unusual taste, diaphoresis). The severity of the reaction was classified as mild, moderate or severe, according to the Brown grading system (17). A risk assessment was performed, as shown in Table I, to divide the patients in "low-medium" and "high" risk.

Allergological work-up

Skin testing (ST), with skin prick test (SPT) and intradermal test (IDT), was performed in all patients according to standard procedures at non-irritating concentrations (2). Patients with positive ST were considered to have an IgE-sensitisation to the drug and were directly referred for DD. On the other hand, patients with negative ST were further stratified according to their risk profile: low-medium risk patients underwent DPT while high risk patients underwent DD due to safety reasons.

DPTs were performed exclusively for the culprit drug, with a 1:2 nurse:patient ratio and with intensive surveillance by expert personnel. When possible, they were organized on the date of the patient's next scheduled visit to avoid overdose or delays (9). A "cautious" protocol was used for all patients. It consisted of several steps at different infusion rates: starting from 1/8 of the final infusion rate reported in each drug package

leaflet and increasing it every 30 minutes. DPT was considered negative if the drug infusion was uneventful, positive in case of an objective reaction. In the first case, the patient could continue with standard infusion by the referring physician, while if the DPT was positive the drug was subsequently administered through DD protocols.

Overall, the allergological work-up was considered "negative" and the patient was delabeled if the DPT was tolerated, "positive" if ST or DPT were positive, "inconclusive" if ST was negative but DPT was not performed for the high-risk profile.

Statistical Analysis

Numerical variables were reported as median (range) while categorical values were reported as n (%). Categorical variables were analysed using the chi-square test or Fisher's exact test as appropriate. Univariate and multivariate logistic regression models were made to evaluate the main outcomes in a predictive fashion. Statistical analysis was performed using Python 3.8.0 version (Anaconda distribution). P values lower than 0.05 were considered statistically significant.

RESULTS

Patients demographics and clinical characteristics of the reactions

A total of 162 patients (F= 148) came to our attention for an immediate reaction to CHT. Mean age was 60 (ranging from 30 to 84) and breast cancer was the most common disease (64/162, 40%). Most of the reactions involved taxanes (paclitaxel 89, docetaxel 7, cabazitaxel 1) and platins (carboplatin 34, oxaliplatin 19, cisplatin 2), while other drugs were less frequently involved; none of the patients were affected by mastocytosis, while mild-moderate asthma was present in 9 patients (11/162, 7%) and only 3 had significant cardiovascular disease (3/162, 2%). More information is displayed in Table 2.

The reactions occurred during the first drug exposure in 90 patients (56%), and as expected, the majority occurring at the first drug administration involved taxanes (76/90, 84%). Conversely, forty patients (40/162, 25%) experienced a reaction during re-exposure after having completed a cycle in previous years, with platins being the most frequent drug (35/40, 88%). Most of the reactions were mild (64/162, 40%) and moderate (68/162, 41%), while severe reactions occurred in a limited number of patients (30/162, 19%). Most reactions

involved the skin (131/162, 80.9%), followed by the respiratory system (84/162, 51.9%) and gastrointestinal tract (48/162, 29.6%). When evaluating the clinical phenotype of the HSRs, most of them had non-specific symptoms and were defined as "either" (77/162, 47.5%), while "type 1" reactions occurred in 48 patients (29.6%), "CRR" in 28 patients (17.3%) and "mixed" reactions in 9 (5.6%) (Table 3).

Skin test results

Skin test resulted negative in most patients (121/162, 74.7%). Amongst the 41 patients with positive ST, 11 had positive SPT (26.8%), while most of them (30, 73.2%) resulted positive at the IDT. Twenty patients (48.8%) had a positive IDT at the 1:100 dilution and 10 patients (24,4%) at the 1:10 dilution. The univariate logistic regression analysis showed that the risk of positive ST was higher in patients who had experienced a reaction to platins (OR 6.4, CI95% 3-13.8, $p<0.001$) and in those who were re-exposed to the drug after a gap (OR 8.1, CI95% 3.6-17.9, $p<0.001$). Additionally, the risk increased at each subsequent infusion (OR 1.4 for each subsequent infusion, CI95% 1.1-1.7, $p<0.005$). Positive ST also correlated with the severity of the reaction (OR 1.8 for each severity grade, CI95% 1.1-2.9, $p=0.02$). Furthermore, there was a positive correlation between ST positivity and "type 1" and "mixed" reaction phenotypes (respectively: OR 2.7, CI95% 1.3-5.7, $p<0.01$, OR 4.1, CI95% 1.04-15.9, $p<0.05$), while the correlation was negative when considering the "CRR" phenotype (OR 0.1, CI95% 0.01-0.66, $p<0.05$). When applying a multivariate logistic regression analysis, ST positivity correlated with reactions to platins (OR 3.5, CI95% 1.2-10.2, $p<0.05$), being re-exposed after a gap (OR 5, CI95% 1.7-14.7, $p<0.005$) and the severity of the reaction (OR 2.6 for each severity grade, CI95 % 1.4-4.7, $p<0.005$).

Drug Provocation Test: short- and long-term outcome

A total of 110 DPT procedures were carried out, all involving patients with negative ST and a low-medium risk profile. Most of the patients who underwent DPT had experienced a reaction to taxanes (78/110, 70.9%) and it had occurred during the first drug infusion (71/110, 64.5%). Furthermore, the majority of these patients had presented with the non-specific "either" clinical phenotype (53/110, 48.1%), followed by the "CRR" (27/110, 24.5%), "type 1" (26/110, 23.6%) and "mixed" phenotype (4/110, 3.6%).

The procedure was uneventful in most patients (98, 89%) and was therefore considered "negative" (Figure 1A). The 12 positive DPT involved paclitaxel (9/12, 75%), oxaliplatin (2/12, 17%) and docetaxel (1/12, 8%). The reactions during DPT were mild (8/12, 67%) or moderate (4/12, 33%) and the phenotype was the same as the initial reaction, except in two patients (one from "type 1" to "either", one from "mixed" to "type 1"). Overall, 10 DPT+ patients continued the drug with DD procedures, while 1 switched to second line therapy and 1 discontinued chemotherapy due to oncological decision. When comparing cases with negative and positive DPT, no differences were found in any of the variables analyzed (age, drug involved, severity, clinical phenotype, previous exposures) (data not shown).

All the 98 patients with a negative DPT continued with standard infusion at the Oncology Unit. At 1 year follow-up, 96 patients (98%) tolerated the infusion without any reactions (Figure 1B). One patient tolerated the first paclitaxel infusion but experienced flushing during the second one. Another patient tolerated three paclitaxel infusions, while the fourth was complicated by urticaria. In the first case ST was not repeated, while ST resulted positive in the second patient. Both continued their first line therapy through DD.

Final diagnosis

After the allergological work-up, most of the patients were delabeled (98/162, 60.5%), of which 68 had experienced a reaction to taxanes (Figure 2). The work-up was considered "positive" in 53 patients (32.7%) and the diagnosis was "inconclusive" only in a minority (11/162, 6.8%), as they had negative ST but did not undergo DPT due to high-risk profile. The univariate logistic regression analysis showed that the probability of being delabeled is higher when the reaction involves taxanes (OR 2.74, CI95% 1.4-5.3, $p<0.005$), occurs during the first drug exposure (OR 1.99, CI95% 1.0-3.8, $p<0.05$) and presents with "CRR" phenotype (OR 6.96, CI95% 2.0-24.2, $p<0.005$). Conversely, the probability of delabeling decreased in patients who reinitiated treatment after a gap (OR 0.28, CI95% 0.1-0.6, $p=0.001$), experienced "type 1" reactions (OR 0.48, CI95% 0.2-0.9, $p<0.05$) and with higher severity (OR 0.33, CI95% 0.2-0.5, $p<0.001$) (Figure 3). When applying a multivariate logistic regression analysis, delabeling correlated directly with "CRR" reactions (OR 6.77, CI95% 1.8-25.1, $p<0.005$) and inversely with being exposed to previous cycles (OR 0.19, CI95% 0.1-0.5, $p<0.001$) and with the higher severity of reaction (OR 0.25, CI95% 0.1-0.4, $p<0.001$).

DISCUSSION

In this study we have identified different subsets of patients experiencing HSRs to CHT. On one side, those who have it during the first drug infusion, mainly involving taxanes, with a "CRR" phenotype and that can be delabeled. On the other side, patients who have reacted to platins, with a "type 1" phenotype, who were previously exposed to the drug, have positive ST and therefore require DDs. This highlights the need of a thorough allergological evaluation aimed at identifying the different mechanisms of these reactions, to manage these patients in the most appropriate way.

The clinical history, starting point of every allergological evaluation, is currently used for risk-assessment and considers the patient's own risk factors and the severity of the reaction. A phenotypical classification based on the symptoms of reactions to oxaliplatin has recently been proposed (16) and other Authors have later applied it to other CHT (11). In our cohort, most of the reactions (47.5%) were classified as "either" due to the presence of non-specific symptoms, followed by "type 1" reactions (29.6%). This differs from what has been described by others (16,11), where the most common phenotype was "type 1", probably due to the different drugs involved, as taxanes are more represented in our cohort than in others, where platins were mostly involved. In line with published data (11), we have shown that "type 1" phenotype correlates with ST positivity and a final diagnosis of hypersensitivity. Furthermore, we have demonstrated that "mixed" phenotype associates with positive ST, while "CRR" correlates with negative ST and a higher probability of being delabeled. Though the large number of "either" phenotypes might question the utility of a phenotypical characterization, the significant correlation between the other phenotypes and the ST results suggests that they may provide early information regarding the outcome of the allergological work-up.

At present, the most utilized diagnostic tool is ST. In our study, the proportion of patients with positive ST (25.3%) was lower than some previously published series (55-45%) (8, 11). This was probably due to the higher number of reactions to taxanes in our study population and in line with the lower number of "type 1" reaction phenotype we have observed. Our data confirmed that positive ST correlates with ADRs to platins and previous exposures to the drug (19, 20), as well as the severity of reaction (21). Notably, ST positivity was also present in a proportion of taxanes-reactive patients (11.3%), similarly to what had been described by *Pagani et al* (21). Though ST positivity has generally been considered a marker of an IgE-mediated mechanism, its meaning in reactions to taxanes is still unclear. In our cohort, most of the patients with ST

positivity to taxanes experienced the reaction during the first infusion. Whether this can be explained by a pre-existing sensitization to *Taxus baccata*, the plant from which paclitaxel derives, is still a matter of debate, especially because specific IgE for paclitaxel have only been isolated once (22). Furthermore, functional studies evaluating basophil degranulation with this type of CHT are limited and involve a low number of patients (11,13).

ST is a specific diagnostic tool but has a low sensitivity (7, 23, 24), thus the gold standard to confirm or rule out hypersensitivity to CHT is DPT. In our study, the large majority of the ST-negative patients who have undergone DPT have tolerated the drug but we were able to identify 11% of patients who experienced a reaction during the test, thus confirming the need to implement DPT to identify all patients requiring DD. Data regarding DPT is limited and the percentage of positive DPT varies amongst different cohorts of patients (6-8, 11, 25, 26); the low number in our population may again be related to the high number of reactions to taxanes, as they accounted for 71% of the procedures. Though a delabeling pathway involving DPT appears to be useful especially for taxanes, it must be noted that we were able to rule out hypersensitivity also in 42% of patients with an ADR to platins. Furthermore, we provided long-term data regarding the following infusions at the Oncology Departments that confirmed drug tolerance in 98% of patients, validating the diagnostic algorithm at least amongst our cohort of patients. Further studies and a higher number of patients are needed to identify possible risk factors for positive DPT.

The single-center design of the study may limit the generalizability of our findings to a broader population or different healthcare settings. However, this study provides a detailed analysis of the diagnostic algorithm used for the management of HSRs to CHT and confirms the utility and safety of implementing DPT to avoid unnecessary DDs.

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Contributions: MP, AM and AV Conceptualization, Data curation, Methodology, Project administration, Writing – original draft; MP, EV, MA and MD Formal Analysis; MP, EV, MA, MD, LC, FM, DL, LL, MCP, SDB, AM and AV Validation, Writing – review & editing.

Conflicts of interest: none

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Figure 1. Short- and long-term outcome of DPT. **A.** Short-term outcome of DPT in low-medium risk patients with negative ST. **B.** Long-term outcome of standard infusion in DPT negative patients

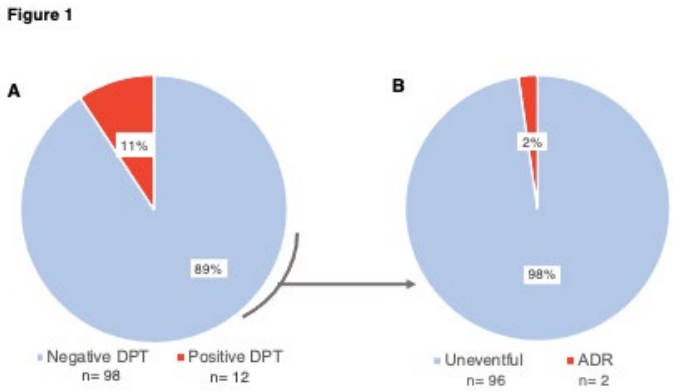

Figure 2. Diagnostic algorithm and results of HSRs to chemotherapy

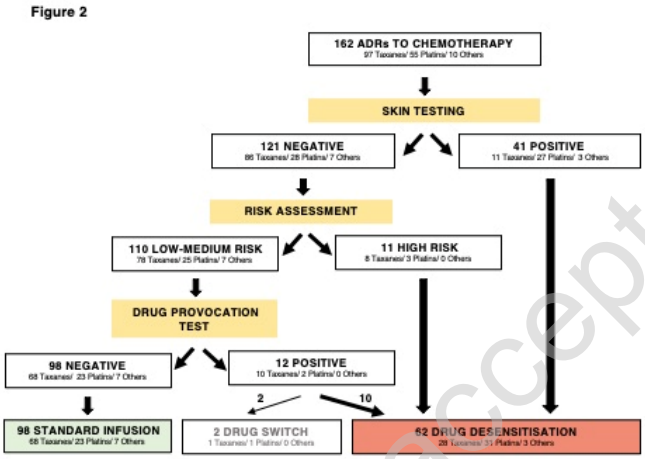

Figure 3. The effect of different clinical variables on the probability of being delabeled. On the right side, clinical characteristics associated with an increased probability of being delabeled; on the left side, those that are associated with a lower probability of delabeling.

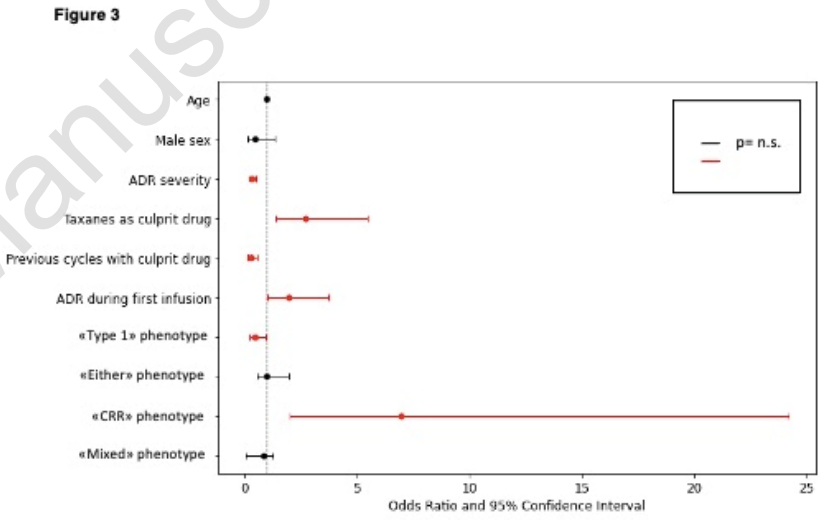

Table 1. Patients' risk profile assessment

	Low-Medium Risk	**High Risk**
Severity of HSR *	Grade 1 or 2	Grade 3
Asthma	Absent/Well controlled	Not controlled
Mastocytosis	Absent	Present
Cardiovascular disease	Absent/Well controlled	Not controlled

*according to Brown classification (2004)

Table 2. Clinical characteristics of the patients who experienced a suspected immediate HSR to CHT.

PATIENTS CHARACTERISTICS	
	Total no. of patients (n=162)
Primary Diagnosis	
Breast cancer	64 (39.5%)
Ovarian cancer	46 (28.4%)
Cervical cancer	13 (8%)
Colorectal cancer	9 (5.5%)
Gastric cancer	9 (5.5%)
Lung cancer	5 (3%)
Prostate cancer	3 (1.8%)
Other	13 (9.9%)
Culprit Drug	
Taxanes	97 (59.9%)
Paclitaxel	89 (54.9%)
Docetaxel	7 (4.3%)
Cabazitaxel	1 (0.6%)
Platins	55 (34%)
Carboplatin	34 (21%)
Oxaliplatin	19 (11.7%)
Cisplatin	2 (1.2%)
Other	10 (6.2%)
Doxorubicin	7 (4.3%)
Cyclophosphamide	1 (0.6%)
Irinotecan	1 (0.6%)
Trabectidin	1 (0.6%)
Comorbidities	
Mild-moderate asthma	9 (7%)
Mastocytosis	0
Cardiovascular disease	3 (2%)

Table 3. Characteristics of the reactions to CHT

HSRs CHARACTERISTICS	
	Total no. of patients (n=162)
Infusion of reaction	
I	90 (55.6%)
II	34 (21%)
III	22 (13.6%)
>III	16 (9.9%)
Previous drug cycles	
No	122 (75.3%)
Yes	40 (24.7%)
Severity (Brown)	
Grade 1	64 (39.5%)
Grade 2	68 (42%)
Grade 3	30 (18.5%)
Symptoms	
Cutaneous	131 (80.9%)
Respiratory	84 (51.9%)
Cardiovascular	19 (11.7%)
Gastrointestinal	48 (29.6%)
Fever/Chills/Backpain	45 (27.8%)
Neuromuscular	3 (1.9%)
Phenotype	
Type 1	48 (29.6%)
CRR	28 (17.3%)
Either	77 (47.5%)
Mixed	9 (5.6%)