Eur Ann Allergy Clin Immunol Vol 54, N.6, 265-276, 2022

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Key elements in hypersensitivity reactions to chemotherapy: experience with rapid drug desensitization in gynaecological cancer in a Tertiary Hospital

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Key words

Adults; chemotherapy hypersensitivity reactions; gynaecological cancer; rapid desensitization; risk factors.

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Doi
10.23822/EurAnnACI.1764-1489.207

Summary

Rapid drug desensitization (RDD) is a procedure performed when no alternative drug is considered equally effective. The aim of our study is to describe the experience with RDD to cytostatics in patients being treated for gynaecological cancer in a Tertiary Hospital, over a period of 5 years. In this paper, we review 22 cases and 107 episodes of RDD; 86.3% of patients had advanced disease and the mortality rate at the time of data collection was 50.0%. RDD was performed on 81.8% patients for platinum, 13.6% for taxanes, and 4.5% for anthracyclines. The reintroduction of antineoplastic drugs in all patients with a previous history of immediate hypersensitivity reaction demonstrated the safety and efficacy of this procedure. There was serious complication (anaphylaxis) in only one case.

Impact statement

This work highlights the safety and effectiveness of antineoplastics.

Introduction

Considering developed countries, the most lethal gynaecological cancer is ovarian, especially high-grade serous carcinoma (1). Ovarian cancer is usually diagnosed at advanced stages (stage III and IV of The International Federation of Gynecology and Obstetrics – FIGO) (1, 2), with 5-year survival rates in all stages reported as low as 50% (3). Platinum-based therapeutic agents are widely used in this subtype, due to a generally good response (1). Other histological types like low-grade serous or clear cell ovarian carcinomas do not show such a good clinical response to these therapies (1) but can still be used in these cases. Platinum sensitivity is described as an absence of relapse for at least 6 months after the last cycle of chemotherapy (4). Nevertheless, platinum agents also play an important role in subsequent relapses of ovarian cancer, as sensitivity is often retained (4). Paclitaxel is often used together with platinum drugs, as this combination improves overall survival in patients with recurrent platinum-sensitive ovarian cancer (5). Platinum-related hypersensitivity reactions (HSR) are reported at a rate of 1 in 10 patients, with higher incidence in advanced stages of the disease (stages III-IV), with serous carcinoma subtype and in the pres-

ence of ascites (5). Multiple cycles of platinum therapies increase the probability of an HSR (4, 5), so desensitization protocols can enhance the chance of retreatment with these drugs and thus increase patient survival.

In developed countries, endometrial cancer is the most common gynaecological malignancy (6). Most of these tumours have a postmenopausal diagnosis and are usually detected at stage I (with > 95% survival rates at 5 years), although they can appear before 40 years of age (6, 7). Nevertheless, if there is locoregional advanced or distant disease, survival rates decrease markedly (8). There are no population-based screening programmes for endometrial or ovarian cancer. Among those with high-risk factors for endometrial tumours, only those with Lynch syndrome have customized screening programmes.

Three of the main histological endometrial cancer subtypes according to the World Health Organization (WHO) include endometrioid, serous, and clear-cell carcinomas (9). Classically and biologically, endometrial carcinomas are divided into 2 types, with type 2 referring to those with typically worse prognosis and including high-grade carcinomas (7, 9).

FIGO classification is used for staging endometrial tumours; the staging is surgical (10). Additionally, a risk group stratification classifies the following cases as a high-risk disease: endometrioid IB G3; stage ≥ II; and non-endometrioid histological subtype (11). Chemotherapy is recommended in endometrioid stage III of FIGO and the approved regime is carboplatin plus paclitaxel. The same therapy is proposed for serous and clear-cell carcinomas (8, 12).

Worldwide, breast cancer is the main cause of cancer-related deaths in women (13). The incidence of breast cancer increases with age (only 25% of cases occur before age 50) and has increased due to the application of national screening programmes with the use of mammography (13). As increasing numbers of breast cancer cases are diagnosed at an earlier stage, the mortality rate has decreased in developed countries in recent years (13). The histological diagnosis is based on WHO (World Health Organization) classification and the eighth edition of the American Joint Committee on Cancer (AJCC) tumour, node, metastases (TNM) staging system. These include biological prognostic information: grade, hormonal receptors, human epidermal growth factor receptor 2 (HER 2) and possibly gene expression (13). Of all the breast cancer subtypes, invasive carcinomas not otherwise specified (NOS) are the most frequent (13).

Hypersensitivity reactions to chemotherapeutic agents

HSRs to a chemotherapy agent are defined as unexpected reactions that cannot be explained by the known toxicity profile of the drug (14). Based on their development mechanism, HSRs are classified as allergic, which involves an immunological mechanism, and non-allergic, when an immunological pathogenic mechanism is not demonstrated (15). The type of allergic reaction is classified into four categories based on the Gell and Coombs classification: type I immunoglobulin E (IgE)-mediated or immediate type; type II cytotoxic-mediated; type III immune complex-mediated; and type IV T cell-mediated or delayed type (16).

Current data indicate that most patients who have experienced HSRs within 24 hours of the last drug administration achieve drug-tolerance with rapid desensitization (15). Immediate drug HSRs usually occur within 1–6 h after the last administration of the drug, and can be IgE-mediated or related to a non-specific histamine release. Non-immediate or delayed reactions can occur at any time from 1 h after the initial drug administration, typically up to 6-12 h. Specifically in cases of chemotherapy, HSRs can occur more than 24 h after drug infusion, probably due to its prolonged half-life, or the administration of premedication drugs, which can mask the acute phase of these reactions (18, 19).

Platinum compounds

Platinum compounds, such as cisplatin, carboplatin and oxaliplatin, are useful antineoplastic agents used in a wide variety of cancers, particularly in gynaecological malignancies (20-22). The first platinum drug approved by the United States Food and Drug Administration (FDA) as an anticancer agent was cisplatin in 1970, with carboplatin being approved almost twenty years later in 1989 (16). These chemotherapy agents are classified as deoxyribonucleic acid (DNA) alkylating agents. However, cisplatin was gradually replaced by carboplatin in patients with ovarian cancer, due to its reduced nephrotoxicity, neurotoxicity and gastrointestinal toxicity (23, 24). Oxaliplatin is a third-generation platinum agent that, similarly to cisplatin and carboplatin, consists of a DNA alkylating agent that forms intrastrand/interstrand DNA crosslinks, affecting DNA base pairing, replication, gene transcription, and cell death (25, 26). The mechanism by which platinum compounds cause HSRs remains unclear, but they are generally reported as being IgE-mediated reactions (16, 24, 27). In the available studies regarding the incidence of HSRs to platinum compounds: cisplatin HSRs range from 1% to 20%; carboplatin HSRs increase with the number of cycles, and range from 1% in those that received ≤ 6 cycles to 27% in those who received ≥ 7 cycles, and up to 47% in those who received ≥ 15 cycles; and oxaliplatin HSRs range from 10% to 25% (26, 28-30). The incidence of cross-reactivity between platinum agents has yet to be clarified, but some studies have documented the cross-reactivity between carboplatin and cisplatin as being higher than 25% (31). The clinical manifestations of HSRs are diverse and unpredictable, varying from only cutaneous manifestations to severe or even fatal manifestations (26, 32).

Taxanes

Similar to platinum compounds, taxanes are an important cause of HSRs in oncologic patients. The most used taxanes are paclitaxel and docetaxel. Paclitaxel is a natural compound, originally

isolated from the bark of the Pacific yew tree, with its antineoplastic effect interfering with the dynamics of microtubules (cytoskeleton), causing mitotic block and cell death (33-35). Docetaxel is a semi-synthetic molecule derived by a taxoid precursor found in European yew trees (35). Due to their low solubility, they are formulated with solvents to allow intravenous administration: Cremophor® EL is associated with paclitaxel and polysorbate 80 with docetaxel (33). These solvents are capable of causing complement activation which leads to anaphylatoxins production and mast cell activation, thereby explaining why some patients experience immediate HSRs (34). Initial studies with taxanes revealed a high incidence of immediate HSRs, which led to the use of premedication with antihistamine and corticosteroids (36). Currently, immediate HSRs to paclitaxel and docetaxel occur in about 10% and 5% of premedicated patients, respectively (36). Immediate HSRs to taxanes occur minutes after starting the infusion during the first or second cycles, and symptoms include flushing, chest, back and abdominal pain, as well as respiratory symptoms (33, 35). Cross-reactivity between paclitaxel and docetaxel exists but seems to vary among different populations and depends on the severity of the initial HSR (32).

Anthracyclines

Anthracyclines, such as doxorubicin, idarubicin, daunorubicin and epirubicin, are used to treat multiple malignancies, interfering with DNA metabolism and ribonucleic acid (RNA) production. HSRs to anthracyclines are rare (32). Clinically, the most important anthracycline that has been well studied, particularly in gynaecological malignancies, is pegylated liposomal doxorubicin (PLD) (32). The reported incidence of immediate HSRs to PLD is 9% (16). This is similar to the incidence of HSRs to taxanes and usually occurs at an interval of 5 minutes after the first cycle, with flushing, back pain and chest tightness as clinical manifestations (16). The mechanism of HSRs is not clear, but it is believed that symptoms derive from complement and mast cell activation (37). Also, interestingly, the free form of doxorubicin does not cause HSRs, with pegylated liposomes being the probable trigger for these reactions (37).

Risk factors to hypersensitivity reactions in chemotherapeutic agents

The main risk factor influencing the occurrence of platinum HSRs is the total number of cycles that patients have received, with the peak of HSRs usually occurring during the 8th or 9th cycle (32). Similarly, other risk factors have been reported, namely a history of atopy and drug allergy; a long platinum-free interval and the administration of ≥ 650 mg of carboplatin (32). The inherited mutations in breast cancer type 1 or 2 genes (Breast Cancer gene – BRCA 1 or 2) appear to be related to a higher risk of reactions to carboplatin infusion and patients are also at risk for these reactions during desensitization (23). On the other hand, the combination of carboplatin with PLD seems to reduce the incidence of HSRs when compared to the administration of isolated carboplatin or its combination with paclitaxel (26). There are studies suggesting that the combination of specific chemotherapeutic drugs may have a predictive value on the HSRs risk (26, 38). Joly *et al.* suggested that the use of carboplatin associated with pegylated liposomal doxorubicin presented a low rate of HSRs, when compared to the combination with paclitaxel, which seems to be associated with a higher number of HSRs, probably due to potentiation secondary to paclitaxel co-administration (26, 38). The predictive factors for HSRs in the case of taxanes remain unclear. However, one study identified that younger age, previous allergy history and a short-course of premedication were associated with paclitaxel HSRs (39). Other comorbidities, such as obesity (body mass index > 30 kg/m^2) have also been associated with an increased risk of HSR to chemotherapy agents (40).

The influence of the presence of eosinophils in allergic diseases is already known, having been studied as a possible risk factor for drug reactions, especially regarding their count in the platinum therapeutic cycle in which the allergic reaction occurred (41). However, some studies carried out in this area have proven an absence of relationship or the presence of a lower number of eosinophils in patients with reactions to platinum salts when compared with non-allergic patients (41).

Rapid drug desensitization

Rapid drug desensitization (RDD) is a procedure performed when no alternative drug in use is deemed equally effective. RDD consists in the induction of temporary unresponsiveness to drug antigens, which allows patients to be treated with medications to which they have previously presented HSRs (42). RDD enables the full therapeutic doses to be reached without major side effects in a relatively short period of time (43). Several desensitization protocols have been published and used for patients with platinum drug HSRs, but most widely accepted desensitization protocols are the 8-step and 12-step, with a duration of 5.8 hours to 8 hours (22, 44, 45). The choice of a specific RDD protocol is based on the risk stratification, according to clinical history and skin test results (46). Various desensitization protocols for taxanes have been studied with the Brigham and Women's Hospital/Dana-Farber Cancer Institute, the 3-bag, 12-step protocol being the most studied as well as having an excellent safety record (32, 47). Regarding the PLD desensitization protocol, data are limited, but the most used protocol is the same as that used for taxanes, consisting of 3 bags and 12 steps (47).

The aim of chemotherapy desensitization is to maintain a temporary tolerance to the chemotherapeutic drug involved in the patient's reaction, which is essential for effective treatment and to achieve the best possible quality of life.

The objective of our study was to describe the experience in rapid drug desensitization to antineoplastic drugs in gynaecological cancers in an Allergy and Clinical Immunology Department of a Tertiary Hospital.

Materials and methods

Study design

The authors performed a retrospective, descriptive and inferential review of patients with gynaecological cancer with a history of HSRs to chemotherapy agents who were submitted to desensitization protocols.

Enrolment took place in a Tertiary Hospital over a period of five years, between June 2015 and June 2020. Patients were included if they had a histologically confirmed diagnosis of gynaecological cancer – ovarian, endometrial or breast, with subtype classification according to WHO guidelines (9, 48) – associated with confirmed HSRs to chemotherapy drugs (defined by European Academy of Allergy and Clinical Immunology – EAACI - guidelines (49)), and who were submitted to RDD. Patients were also required to be ≥ 18 years of age and able to provide written informed consent before each desensitization.

This paper was written considering the ethical and legal principles and in accordance with the recommendations of the Declaration of Helsinki of the World Medical Association. The anonymity of all the participants of this work was guaranteed.

Subjects

Patients included were those referred to the Allergy and Clinical Immunology Department by the Gynaecology Department, with immediate-type HSRs to chemotherapy drugs and an absence of possible alternatives, and who were eligible for allergy diagnostic work-up and RDD. Patients with delayed reactions (> 24 hours) were excluded, such as drug-induced fever and exfoliative skin reactions as multiform erythema, Stevens-Johnson syndrome or toxic epidermal necrolysis. Type II and III reactions (Gell and Coombs) were also excluded.

Immediate HSRs were classified according to Brown's grading system (BGS) (50) as: 1) Mild (grade I), corresponding to symptoms limited to the skin or involving a single organ/system; 2) Moderate (grade II), corresponding to symptoms involving at least two organs/systems without a significant drop in blood pressure or in oxygen saturation; 3) Severe (grade III), corresponding to symptoms involving at least two organs/systems and a significant drop in blood pressure or in oxygen saturation. Organs/systems signs and symptoms of HSRs were defined as mucocutaneous (flushing, pruritus, urticaria, angioedema), respiratory (nasal symptoms, dyspnoea, wheezing, oxygen desaturation, bronchospasm, throat or chest tightness), cardiovascular (chest pain, tachycardia, lipothymia, syncope, and hypotension), gastrointestinal (nausea, vomiting, diarrhoea, and abdominal pain) and other symptoms (altered state of consciousness, headache, paraesthesia, pain).

Disease characteristics and outcomes

Patients were characterized according to demographic data, history of atopy, age at diagnosis of gynaecological cancer, histological subtype of cancer, staging, distant metastases at diagnosis, drug and therapeutic cycle involved in HSR, time interval between cycles, Brown's grading system (BGS) (50) of HSR, drug chosen for RDD, number of therapeutic cycles in RDD, complications of RDD, the therapeutic success of RDD and mortality.

Assessment of allergy diagnosis

Each patient was evaluated with a detailed clinical history. Personal and family history of atopy were also considered.

All patients underwent skin tests for the suspected chemotherapeutic agent and latex at least 4 weeks after the initial reaction, according to The European Network for Drug Allergy/EAACI recommendations (49), with the exception of a single case of anthracycline reaction, where RDD was based only on clinical history due to the absence of standardization skin test concentrations. Skin prick tests (SPT) were performed with undiluted agents – carboplatin (10 mg/mL), cisplatin (1 mg/mL) (49), paclitaxel (6 mg/mL) and docetaxel (1 mg/mL) (51). When SPT were negative, intradermal tests (IDs) were performed with a 1/10 dilution and additional dilution in cases with moderate and severe reaction (grade II and III (50)). Immediate readings were performed at 15-20 minutes for SPT and IDs (49). A weal of ≥ 3 mm in diameter for SPT or an increase in diameter of the initial ID of ≥ 3 mm were defined as a positive result, when observed a negative response to control solution (0.9% saline) and a positive response to histamine (10 mg/mL) (49).

Desensitization protocol

A 12-step protocol, described by Castells *et al.* (42) was implemented, with three dilutions of the target drug dose, containing 1/100, 1/10, and 1/1, respectively, diluted in 250 mL of 0.9% saline solution.

All desensitization procedures were conducted on an inpatient regimen and were performed using premedication: clemastine 2 mg, intravenously; ranitidine 50 mg, intravenously, and montelukast 10 mg, per os, maintaining the premedication proposed by oncology according to the drug or the protocol used. Based on our experience and adapted from the literature, our RDD protocols include premedication administration 30 minutes before starting the procedure, with the exception of montelukast, which was administered in 2 steps: 12 h and 30 minutes before the procedure (52).

Angiotensin-converting enzyme inhibitors and beta-adrenergic blockers were retained for 24 hours before desensitization.

The treatment of adverse drug reactions depended on the severity: mild reactions were treated with cetirizine (10 mg administered per os), and moderate-severe/recurrent reactions were treated with clemastine (2 mg intravenously or intramuscularly), ranitidine (50 mg administered intravenously), and methylprednisolone sodium succinate (1-2 mg/kg administered intravenously). Bronchospasm was also treated with inhaled beta2 agonists (salbutamol or ipratropium bromide). In anaphylactic reactions, epinephrine (0.01 mg/kg intramuscular at the dilution of 1 mg/mL) was administered, corresponding, in our sample, to 1 case.

Upon resolution, infusion was continued at the current step, or at a previous step, depending on the severity of the reaction (53).

Statistical analysis

Statistical analysis was performed using SPSS Statistics version 24.0®. Descriptive statistics were analysed as mean and standard deviation for the variables with normal distribution, and median and interquartile range for variables without normal distribution.

Results

Demographic and clinical characteristics

Twenty-two women with HSRs to chemotherapy agents were submitted to RDD, corresponding to 107 RDD procedures (mean 4.9 ± 4.5 procedures per patient). The mean age of the study cohort at the time of the first desensitization was 56.5 ± 14.3 years, ranging from 22 to 77 years old. Obesity (defined as body mass index > 30 kg/m^2) was observed in 31.8% (n = 7) and history of atopy was confirmed in 27.2 % (n = 6) patients: confirmed drug allergy history (nonsteroidal anti-inflammatory drugs) in n = 3 patients; allergic asthma and rhinitis in n = 2 patients; food allergy in n = 1. One third (n = 2) of the patients with a positive history of atopic disease had also a history of family atopy (allergic asthma or penicillin allergy).

Patient characteristics are summarized in **table I**.

Cancer diagnosis

Regarding diagnosis, the mean age of cancer diagnosis was 51.5 ± 12.8 years, ranging from 22 to 69 years old. Most of the patients (77.3%, n = 17) had advanced disease (stage III or IV) at the time of diagnosis. The types and subtypes of primary cancer are summarized in **table II**.

When retrospective data were collected, half of the patients, corresponding to n = 11, had already died due to disease progression. Of this group of patients, only one had a disease-free survival interval of more than one year. Considering patients diagnosed until 2015 (40.9%, n = 9), the 5-year survival rate was 55.6% (n = 5 of total n = 9).

Only 1 patient presented a BRCA 1 pathogenic mutation: a high-grade serous ovarian cancer and cisplatin HSR (patient number 16). Another patient presented a BRCA 2 variant of undetermined significance (VUS), this one with a low-grade serous ovarian cancer and carboplatin HSR (patient number 3); these two patients presented different severity of HSRs (grade III in patient number 16 and grade I in patient number 3).

Hypersensitivity reactions and desensitization

These data are summarized in **table I** and time intervals between lines of treatment are shown in **figure 1**, by patient and drug. Clinical manifestations of HSRs are illustrated in **figure 2**.

Platinum compounds: most patients (81.8%, n = 18) presented HSRs to platinum salts: 88.9% (n = 16 of total n = 18) to carboplatin and 11.1% (n = 2 of total n = 18) to cisplatin. Regarding comorbidities, one third of the patients (n = 6 of the total n = 18) were obese and 22.2% (n = 4 of the total n = 18) had atopy. According to BGS (50), HSRs were characterized as grade I in 27.8% (n = 5 of total n = 18), grade II in 5.6% (n = 1 of total n = 18) and grade III in 66.7% (n = 12 of total n = 18). The first episode of HSR to platinum occurred at a median 13.0 cycles (minimum 5 cycles, maximum 19 cycles). Almost all patients (94.4%, n = 17 of total n = 18) experienced the HSR in a number of cycles ≥ 7. The median platinum dose in the HSR cycle was 527.2 mg ± 161.2 mg, corresponding in 22.2% (n = 4 of total n = 18) to a dose ≥ 650 mg. Median blood eosinophil count before the administration of the HSR cycle was 98.3 cells/µl (minimum 0 cells/µl, maximum 300 cells/µl).

In patients diagnosed with ovarian cancer, the median time interval between the HSR and previous chemotherapy cycle was 10.7 months (minimum 2 months, maximum 23 months), and in 1 patient with ovarian cancer (patient number 15) platinum HSR occurred during the first group of cycles (5th cycle).

In patients diagnosed with endometrial cancer, the median time interval between the HSR and previous chemotherapy cycle was 49.0 months (minimum 8 months, maximum 144 months). In 1 patient with endometrial cancer (patient number 5) platinum HSR occurred during the first group of cycles cycle (8th cycle).

In 50.0% (n = 9 of total n = 18) of platinum chemotherapy HSRs, patients were under treatment with placlitaxel (skin tests confirmed platinum hypersensitivity).

Skin prick tests (SPT) with platinum compounds were positive in 38.9% of the patients (n = 7 of total n = 18), all to carboplatin (n = 4 grade III and n = 3 grade I). In all patients with positive SPT, IDs were not performed due to a significant risk of HSRs associated to the procedure. ID tests were positive in 55.5% (n = 10 of total n = 18), n = 7 carboplatin and n = 2 cisplatin (n = 1 grade I; n = 2 grade II; n = 6 grade III). Evidence of skin test cross reactivity had been presented in 4 patients (n = 2 cisplatin, n = 2 carboplatin).

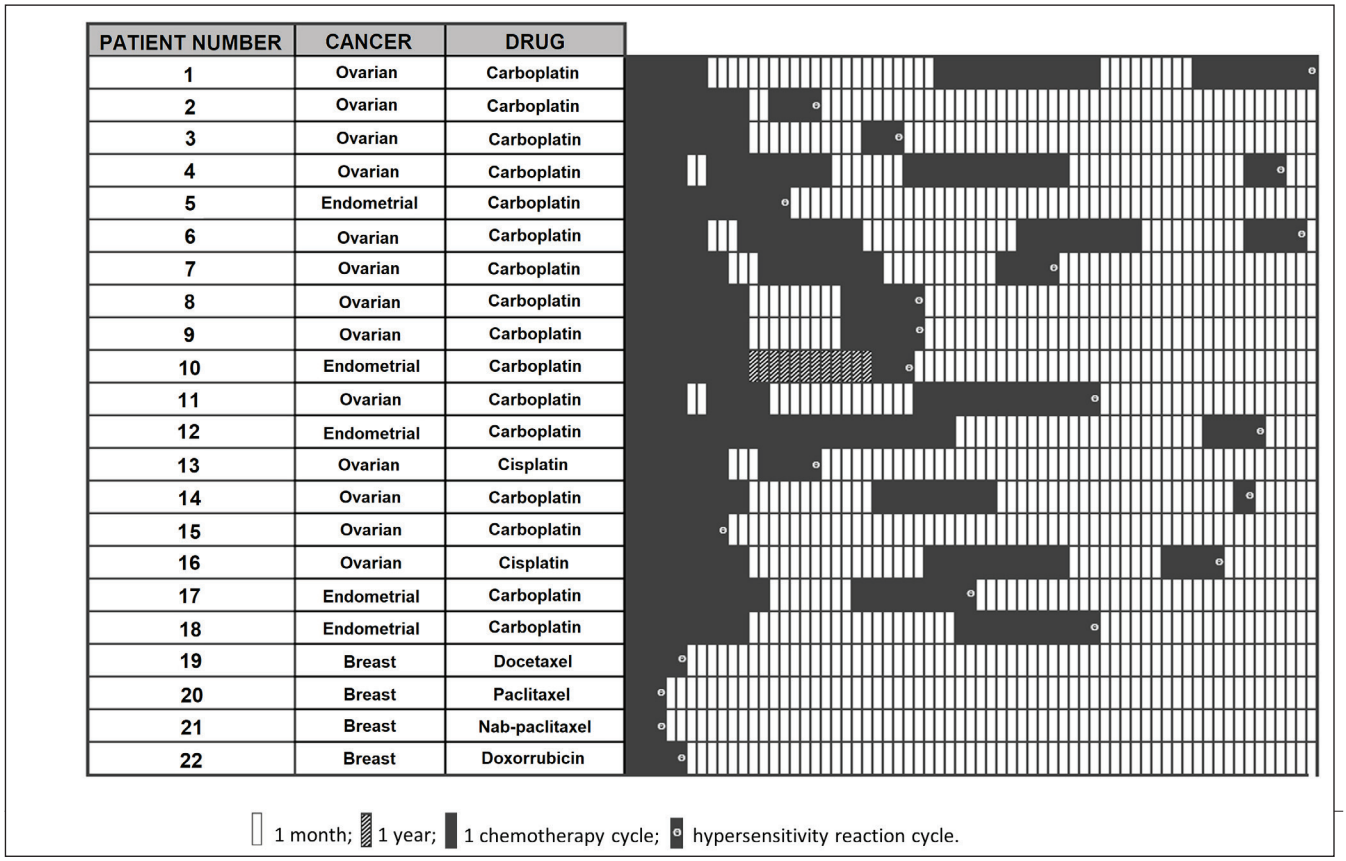
RDD was performed in all patients with the respective drug involved in the HSR, after workup through skin tests (**table I**). The median number of RDD cycles was 3.5 cycles (minimum 1 cycle; maximum 24 cycles). Complications during RDD occurred in one third of the patients (n = 6 of total n = 18), almost all grade I reactions, namely pruritus, facial flush and urticaria. In one case (patient number 14, **table I**), a severe type III reaction occurred, corresponding to anaphylactic shock during infusion of the eleventh step (third bag – highest concentration). In this case, intramuscular epinephrine, intramuscular clemastine, intravenous methylprednisolone and inhaled beta2 agonists were required. This patient had a type III reaction as inaugural HSR and positive SPT for carboplatin. The following desensitization protocol was adjusted to 15 steps, with only a type I reaction registered.

Table I *- Patient characteristics.*

Patient	Age of rdd	Obesity	Atopy	Familiar atopy	Cancer	Drug	Skin tests	HSR cycle	HSR cycle ≥ 7	BGS	Platinum dosis (mg)	Eosinophils (cells/mL)	RDD cycles	RDD complications	Complete scheme	Mortality
1	22	Yes	Yes	No	Ovarian	Carboplatin	**Positive** (Prick 1:1) Cisplatin positive (Prick 1:1)	18	Yes	III	850	100	4	Yes (I)	Yes	Yes
2	50	No	No	No	Ovarian	Carboplatin	**Positive** (Prick 1:1) Cisplatin negative	8	Yes	III	650	100	6	No	Yes	Yes
3	33	No	No	No	Ovarian	Carboplatin	**Positive** (ID 1:10) Cisplatin negative	8	Yes	I	645	30	2	No	Yes	No
4	65	No	No	No	Ovarian	Carboplatin	**Positive** (ID 1:100) Cisplatin negative	19	Yes	III	600	100	7	No	Yes	Yes
5	68	Yes	Yes	Yes	Endometrial	Carboplatin	**Positive** (ID 1:100) Cisplatin negative	8	Yes	III	600	0	2	Yes (I)	Yes	No
6	73	Yes	No	No	Ovarian	Carboplatin	**Positive** (Prick 1:1) Cisplatin negative	19	Yes	I	550	300	24	Yes (I)	Yes	Yes
7	54	No	No	No	Ovarian	Carboplatin	**Negative** (Carboplatin and cisplatin)	14	Yes	III	500	0	3	Yes (I)	Yes	Yes
8	56	Yes	No	No	Ovarian	Carboplatin	**Positive** (ID 1:100) Cisplatin negative	10	Yes	III	500	0	4	No	Yes	Yes
9	44	No	No	No	Ovarian	Carboplatin	**Positive** (Prick 1:1) Cisplatin positive (Prick 1:1)	10	Yes	I	500	200	3	No	Yes	Yes
10	77	No	No	No	Endometrial	Carboplatin	**Positive** (Prick 1:1) Cisplatin negative	8	Yes	I	460	0	5	No	Yes	No
11	50	Yes	Yes	No	Ovarian	Carboplatin	**Negative** (Carboplatin and cisplatin)	15	Yes	III	425	300	3	Yes (I)	Yes	No
12	73	No	No	No	Endometrial	Carboplatin	**Positive** (ID 1:10) Cisplatin negative	19	Yes	II	315	140	1	No	Yes	No
13	43	No	Yes	Yes	Ovarian	Cisplatin	**Positive** (ID 1:10) Carboplatin positive (ID 1:10)	8	Yes	III	130	100	6	No	Yes	Yes
14	49	No	No	No	Ovarian	Carboplatin	**Positive** (Prick 1:1) Cisplatin negative	13	Yes	III	700	100	6	Yes (III)	Yes	Yes
15	41	No	No	No	Ovarian	Carboplatin	**Positive** (Prick 1:1) Cisplatin negative	5	No	III	550	100	3	No	Yes	Yes
16	68	No	No	No	Ovarian	Cisplatin	**Positive** (ID 1:10) Carboplatin positive (ID 1:10)	16	Yes	III	430	100	6	No	Yes	No
17	70	No	No	No	Endometrial	Carboplatin	**Positive** (ID 1:10) Cisplatin negative	13	Yes	III	685	0	2	No	Yes	No
18	70	Yes	No	No	Endometrial	Carboplatin	**Positive** (ID 1:10) Cisplatin negative	13	Yes	I	400	100	3	Yes (I)	Yes	No
19	53	No	Yes	No	Breast	Docetaxel	**Positive** (ID 1:10)	3	No	III	N/A	200	4	No	Yes	No
20	53	Yes	No	No	Breast	Paclitaxel	**Negative**	2	No	III	N/A	0	5	No	Yes	No
21	66	No	Yes	No	Breast	Nab-paclitaxel	**Negative**	2	No	III	N/A	0	3	No	Yes	No
22	65	No	No	No	Breast	PLD	N/A	3	No	III	N/A	0	5	No	Yes	No

BGS: Brown's grading system; HSR: hypersensitivity reactions; ID: Intradermal tests; PLD: Pegylated liposomal doxorubicin; N/A: not applicable; RDD: Rapid drug desensitization.

Figure 1 *- Time intervals between groups of cycles, according to patient and drug. The patient number is matching with table I.*



PATIENT NUMBER	CANCER	DRUG
1	Ovarian	Carboplatin
2	Ovarian	Carboplatin
3	Ovarian	Carboplatin
4	Ovarian	Carboplatin
5	Endometrial	Carboplatin
6	Ovarian	Carboplatin
7	Ovarian	Carboplatin
8	Ovarian	Carboplatin
9	Ovarian	Carboplatin
10	Endometrial	Carboplatin
11	Ovarian	Carboplatin
12	Endometrial	Carboplatin
13	Ovarian	Cisplatin
14	Ovarian	Carboplatin
15	Ovarian	Carboplatin
16	Ovarian	Cisplatin
17	Endometrial	Carboplatin
18	Endometrial	Carboplatin
19	Breast	Docetaxel
20	Breast	Paclitaxel
21	Breast	Nab-paclitaxel
22	Breast	Doxorrubicin

Figure 2 *- Signs and symptoms of chemotherapy hypersensitivity reactions according drug class.*

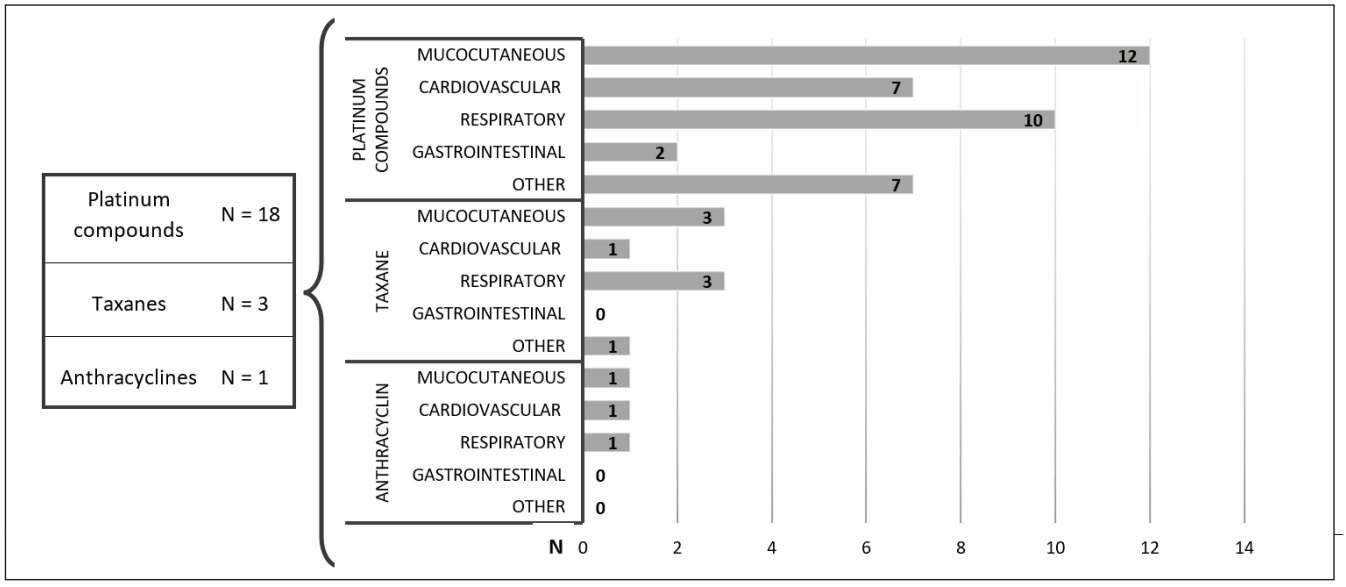


Table II *- Characterization of types and subtypes of primary cancer organ. The patient number is matching with table I.*

Patient Number	Type of gynecological cancer	Age at diagnosis	BRCA mutation/ Lynch syndrome	FIGO staging	Distant metastasis at diagnosis	Disease progression	Age of death
	Ovarian cancer						
9	High-grade serous	41	No	IIIC	No	Yes	44
6	High-grade serous	66	No	IIIC	No	Yes	78
11	High-grade serous	47	No	IIIB	No	Yes	N/A
2	High-grade serous	47	No	IIA	No	Yes	51
16	High-grade serous	65	BRCA 1	IIIA1	No	No	N/A
13	High-grade serous	42	No	IIC	No	Yes	45
7	High-grade serous	49	No	IIIC	No	Yes	55
8	High-grade serous	53	No	IVA	Pleura	Yes	64
14	High-grade serous	44	No	IIIA1	No	Yes	54
3	Low-grade serous	30	VUS in BRCA 2	IIC	No	Yes	N/A
4	Clear-cell	61	No	IIB	No	Yes	68
15	Clear-cell	38	No	IIIC	No	Yes	42
1	Juvenile granulosa cell tumour	22	No	IC2	No	Yes	32
	Endometrial cancer						
18	Endometrioid grade 2	64	No	IIIB	No	Yes	N/A
12	Endometrioid grade 3	69	No	IVA	No	Yes	N/A
17	Endometrioid grade 3	66	No	IVB	Lung	Yes	N/A
10	Serous	65	No	IIIA	No	Yes	N/A
5	Clear-cell	67	No	IVB	Gastric	Yes	N/A
	Breast cancer			**AJCC staging**			
22	Invasive carcinoma NOS (Luminal B like - HER2 negative)	45	No	IA	No	Yes	N/A
21	Invasive carcinoma NOS (Luminal B like - HER2 negative)	51	No	IV	Liver, Pleura, Bone	Yes	N/A
20	Invasive carcinoma NOS (Triple-negative)	48	No	IIIB	No	Yes	N/A
19	Invasive carcinoma NOS (Luminal B like - HER2 negative)	53	No	IV	Lung, Bone	Yes	N/A

AJCC: American Joint Committee on Cancer; BRCA: Breast Cancer gene; FIGO: International Federation of Gynecology and Obstetrics; N/A: not applicable; NOS: not otherwise specified; HER2: Epidermal growth factor receptor 2; VUS: variant of unknown significance.

All patients completed the proposed chemotherapy desensitization protocol.

Taxanes: this was the second most frequent group of chemotherapy drugs that resulted in HSRs and RDD in our sample, corresponding to a total of 13.6% (n = 3) of patients (n = 1 to docetaxel, n = 1 to nab-paclitaxel and n = 1 to paclitaxel). The three patients were initially diagnosed with advanced breast cancer by 2015, resulting in a 5-year survival rate of 100.0%. Regarding comorbidities, two patients presented atopy and one patient was obese.

HSRs in this group occurred at an early stage of the chemotherapy regimen (minimum 2, maximum 3 cycles), and all patients had a grade III HSR.

Considering the patient with HSR to docetaxel, SPT were positive for ID 1:10. The patients with paclitaxel and nab-paclitaxel HSRs had negative SPT for the respective drug.

The median number of RDD cycles was 4.0 (minimum 3 cycles, maximum 5 cycles) and none of the patients experienced complications during the RDD cycles.

All patients completed the proposed chemotherapy desensitization protocol.

Anthracyclines: only one patient suffered from HSR (patient number 22, **table II**) to PLD and underwent RDD. The patient had a diagnosis of non-metastatic breast cancer and presented no other diseases/comorbidities. HSR occurred in the 3rd cycle and was characterized as severe (grade III). No skin tests were performed. The patient underwent 5 cycles of RDD without complications, and has a current disease-free survival of 3 years.

Discussion

In this study we report the experience of our hospital in 107 successful RDD performed in 22 patients who experienced immediate type HSRs to platinum compounds, taxanes, and anthracyclines. Only one patient experienced a severe complication (HSR grade III) during the first 12-step RDD, which was subsequently changed to a 15-step protocol with no complications.

It is well established that any chemotherapy agent can cause HSRs; however platinum and taxanes are the most common agents involved in HSRs and our results are in accordance with this (54). Most of our patients presented HSRs to platinum agents, and this is also partly justified by the wide use of this group in the first line of treatment of solid tumours in adults, especially for ovarian cancer.

The difference in the median time interval between the HSR and previous chemotherapy cycle in ovarian and endometrial cancer is related to the fact that there is a higher rate of relapse in the former.

In taxanes, the HSRs occurred despite Ginecology-Oncology premedication protocol, that includes: dexamethasone 10 mg and H1 and H2 antihistamines (clemastine 2 mg, ranitidine 50 mg), in the cases of paclitaxel and nab-paclitaxel (55); dexamethasone 8 mg (on the day before, the day of the treatment and the day after), in the case of docetaxel (55, 56).

The patients selected for desensitization were those who had immediate HSRs and, therefore, the mechanism likely to be implied is based on IgE-induced sensitization, although skin tests did not confirm this in all patients, as in other published series (57). In our study, the patients selected for RDD were those with a clinical history compatible with immediate HSRs and positive SPT; and in patients with negative SPT, only those diagnosed with a more severe immediate HSRs - grade III.

Premedication for platinum includes antiemetic drugs and dexamethasone, and there is no premedication prescribed in the case of PLD (55).

Most patients in the three types of cancer had an advanced stage of the disease at the time of diagnosis, which generally requires higher doses of chemotherapy, a greater number of cycles and consequently increased chances of HSRs, and these are well established risk factors for HSRs to platinum compounds (32).

Taking into account previous investigations in which it was reported that a drug allergy history correlated with predictive risk of chemotherapy allergy (32, 58), especially with platinum compounds, our sample showed a low prevalence, not only regarding previous drug allergy history but also other atopic diseases, when compared to other results in the literature (5). The presence of obesity has been associated with severe manifestations and fatal outcomes in anaphylaxis (59, 60). In our sample, obesity was also present in a significant number of patients, not only in the platinum group, but also for taxanes, considering that almost half of these patients presented severe grade III HSRs. These data highlight obesity as a possible predictor of chemotherapy HSRs, although further studies are needed with a larger sample size.

The association of paclitaxel with platinum chemotherapy schemes improves overall survival in patients with recurrent platinum-sensitive ovarian cancer (5). Our work has also shown that this association was very prevalent, corroborating that the combination of these drugs is considered a risk factor (26).

Although pathogenic mutations in BRCA 1/2 appear to increase the risk of HSRs to carboplatin infusion (23), our population showed a low prevalence of this mutation which was confirmed in only one woman with a cisplatin HSR. The other woman with VUS BRCA 2 mutation had a carboplatin HSR. These patients also presented heterogeneity in HSR severity, with the pathogenic variant associated with a higher-grade reaction (III).

The relationship between the presence of eosinophils and allergic diseases is already known, and has been studied as a possible risk factor in drug HSRs, especially regarding their count in the specific platinum therapeutic cycle in which the allergic reaction occurred (61). However, some studies carried out in this area have proven an absence of relationship or even the presence of a lower number of eosinophils in patients with platinum reactions (41), as shown in our data.

In the platinum compounds HSR cases, almost the entire sample (n = 17, total n = 18) presented HSRs after ≥ 7 cycles of che-

motherapy, which is in keeping with the number of cycles being considered a risk factor for allergic reactions (32). The same is not true for the other groups of drugs studied, which is also in agreement with the literature (16, 33).

The positive skin tests did not correlate with the severity of the initial reaction, as there were cases in which the tests were positive and the HSR was mild (grade I) and cases in which the tests were negative and the HSRs were severe (grade III). Although platinum skin tests are recommended and negative test results are associated with a lower risk of anaphylaxis (45, 62), all patients in our sample with negative skin tests had severe type III reactions, so RDD was performed in accordance to the risk assessed via clinical history. Even considering that platinum skin tests are recommended and validated, and are a useful complementary diagnostic tool, this must always be associated with a complete and exhaustive clinical history to assess the risk of a future desensitization procedure.

Skin tests for paclitaxel showed negative results in all tested cases, which is in line with data presented in literature, corroborating that the predictive value has not yet been demonstrated (63).

The high mortality rate of our sample (50.0%) is justified by advanced oncological disease at the date of the first HSR to chemotherapy. The same may justify the fact that, in the case of platinum salts, in which a higher dose is associated with an increased risk of HSRs, the vast majority of patients had been submitted to multiple treatment lines.

Conclusions

In all presented cases, rapid drug desensitization successfully allowed the reintroduction of antineoplastic drugs in patients with a previous history of immediate hypersensitivity reaction. Of all patients included, only one had a serious complication (anaphylaxis) during the course of the desensitization protocol, and it was necessary to adjust the protocol from 12 to 15 steps in the following cycles.

A joint protocol between the departments of gynaecology and allergy and clinical immunology allows the patients to benefit from better clinical guidance, resulting in the conclusion of the proposed chemotherapy in cases of HSRs.

Our work demonstrated the safety and effectiveness of these protocols, highlighting the advantages of gaining experience in this procedure.

Conflict of interests

The authors declare that they have no conflict of interests.

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