

PLATINUM HYPERSENSITIVITY REACTIONS, A FOCUS ON DESENSITISATION

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Abstract

Platinum-based chemotherapy is the standard of care in a wide array of cancers. All chemotherapy, including platinum derivatives, can cause hypersensitivity reactions which greatly limit their use due to the risk of anaphylaxis, forcing oncologists to use alternative chemotherapy, sometimes with a lower efficacy. The exact pathogenesis of platinum hypersensitivity reactions remains unknown, a type I mechanism is most frequently involved; however, type II, III, IV, or mixed mechanisms have also been described. Patients with atopy, a long platinum-free interval, treatment in palliative setting and higher cumulative dose are at risk of hypersensitivity. For these patients, desensitization protocols are available to treat allergic reactions to various agents, including platinum chemotherapy. Desensitization promotes antigen tolerance and allows the safe and efficient administration of the agent responsible for the hypersensitivity reaction. This review aims at providing insight into the current knowledge of platinum hypersensitivity with focus on available desensitization protocols.

Rezumat

Chimioterapia pe bază de platină este piatra de temelie în tratamentul unei game variate de cancer. Toate chimioterapicele, inclusiv derivații de platină, pot provoca reacții de hipersensibilitate care limitează mult utilizarea lor datorită riscului de șoc anafilactic, obligându-i pe oncologi să utilizeze protocoale alternative de tratament, uneori cu o eficacitate mai redusă. Patogeneza exactă a reacțiilor de hipersensibilitate la platină rămâne necunoscută, cel mai frecvent este implicat un mecanism de tip I; cu toate acestea, au fost descrise și mecanisme de tip II, III, IV sau mixte. Pacienții cu atopie, interval liber de platina prelungit, tratament cu intenție paliativă și doză cumulată de platină mai mare prezintă un risc crescut de hipersensibilitate. Pentru acești pacienți, sunt disponibile protocoale de desensibilizare care permit combaterea reacțiilor alergice la diferiți agenți, inclusiv chimioterapicele pe bază de platină. Desensibilizarea promovează toleranța la antigen și permite administrarea sigură și eficientă a agentului responsabil de reacția de hipersensibilitate. Acest *review* își propune să ofere o trecere în revistă a datelor actuale cu privire la hipersensibilitatea la platină, cu accent pe protocoalele de desensibilizare disponibile.

Keywords: platinum hypersensitivity, desensitization, allergic reaction

Introduction

Cytotoxic chemotherapy may cause a wide range of adverse events that vary from gastrointestinal symptoms, cardiovascular toxicity, skin toxicity, cytopenia to severe hypersensitivity reactions (HSR) and anaphylaxis. Hypersensitivity reactions are serious, unexpected treatment complications that have been described for almost all chemotherapeutic agents and significantly limit their use. The clinical manifestations of HSR can range from mild symptoms as pruritus, urticaria, flushing to severe dyspnoea, hypotension, tachycardia

and even death. Hypersensitivity reactions are classified as type I immediate immunoglobulin E (Ig E) mediated, type II antibody-mediated, type III immune complex-mediated and type IV delayed or T-cell mediated HSR [76]. Chemotherapy-induced hypersensitivity reactions are complex and not completely understood. Even though most reactions are consistent with type I, Ig E - mediated reactions, some drugs may induce mixed hypersensitivity reactions with two or more involved mechanisms [13]. Platinum-based chemotherapy is the backbone of systemic therapy in a wide range of cancers, including, but not limited to

gynaecologic [48, 49, 54], gastrointestinal [10, 12] and lung cancer [3, 50] for both adult and paediatric [67] patients. They represent a standard of care both in the first-line setting, but also for recurrent disease. Although they are efficient, generally well-tolerated chemo-therapeutic agents with manageable side-effects, their use is frequently restricted because of hypersensitivity reactions.

Incidence & risk factors

Hypersensitivity reactions induced by chemotherapy are an important subgroup of drug-related adverse events that are unpredictable and may display various clinical symptoms, in some cases leading to anaphylaxis, cardiovascular collapse and death. An epidemiological analysis of fatal anaphylaxis in the United States from 1999 - 2010, placed anticancer therapy as the third leading cause of fatal drug-related anaphylactic reactions [27]. Cisplatin HSR frequency varies from 5 - 20% [16] and increases with the number of administrations, as well as with the association of concurrent radiotherapy [10, 33]. However, the number of cisplatin cycles is generally limited to 4 - 6 administrations due to other limiting toxicities, and therefore cisplatin-induced HSR occurs less often.

Carboplatin is a second-generation platinum derivate, and similar to cisplatin, the risk of HSR greatly varies with the number of administered cycles. Allergic reactions rarely appear during the first cycle, and they occur in < 1% for less than five administrations [71]. Nevertheless, for patients receiving seven or more administrations, the risk increases greatly to over 27% [45]. Furthermore, the existence of a platinum-free interval greater than six months and the administration of platinum compounds in the second or third-line setting raises the risk of allergic reactions up to 44% [53]. The cumulative carboplatin dose is linked to the risk of HSR; higher lifetime doses were associated with higher risk [55].

For oxaliplatin, an allergic reaction occurs in around 12% of cases. Most HSR are mild to moderate, with 1% of the patients presenting with severe, life-threatening reactions. Similar to carboplatin related HSR, oxaliplatin allergic reactions are more frequent in the second line and the palliative setting [4]. Patients treated in the first line with other compounds, particularly irinotecan had a higher risk of HSR compared to those treated in the first-line setting [70]. The number of administrations prior to the allergic reaction episode varies, but is similar to other platinum compounds ranging from 7 - 9 cycles. The time interval from starting the infusion to the onset of the hypersensitivity reaction varies from 10 min to 4 hours, with severe reactions occurring more frequently in the first 10 min [32, 62].

A pre-existing allergic background is associated with a higher frequency of HSR. Patients presenting chemotherapy-induced allergic reactions have an increased

incidence of atopy compared to the general population, of 44% [39, 46]. Although better outlined for the paediatric population, the administration schedule is another important factor, weekly administrations being linked to higher risk [81]. Moon *et al.* showed that the presence of breast cancer (BRCA) gene 1 and 2 mutations increase the risk for HSR by 43% [52]. Also, the cytotoxic chemotherapy agent administered with the platinum compound influences the risk of HSR. Data from the CIG CALYPSO trial showed that the association of carboplatin with paclitaxel is linked to a higher incidence of allergic reactions compared to liposomal doxorubicin [28]. A history of an allergic reaction to a specific platinum compound is linked to a greater risk of HSR to different platinum treatments, as switching platinum salts was not yet proved to be an efficient alternative [9].

Many of the oncological patients uses "supplements", which are considered harmless due to their natural origin. In fact, some of them could enhance the effect of chemotherapy (for cisplatin for example), but in the most of the cases it could increase the risk of an allergic reaction [69].

Mechanism

The exact pathogenesis of platinum induced hypersensitivity reaction remains mostly unknown. However, it is generally regarded to be primarily an Ig E - mediated process. Type I, Ig E-mediated hypersensitivity reactions, require a prior sensitization period. Ig E bind to mast cells and basophils, leading to the release of various cytokines such as histamine, leukotrienes and prostaglandins [58] which leads to the early onset of symptoms such as pruritus, chest pain, rash, and in some rare cases severe anaphylactic reactions. Type II allergic reactions have been reported for oxaliplatin with the production of anti-platelets and anti-erythrocytes directed antibodies, leading to immune thrombocytopenia and haemolytic anaemia [21, 43, 62]. Additionally, type III HSR, leading to joint pain, proteinuria or chronic urticaria have been described for oxaliplatin [44].

Recent data suggest the possibility of type IV, T cell-mediated hypersensitivity reactions to platinum compounds. The activated T helper cells cause a delayed inflammatory response, that may become clinically evident even days after the initial administration. Carboplatin and cisplatin are more frequently associated with delayed reactions, and most patients present with mild cutaneous manifestations such as maculopapular rash or eczema; however these patients are at risk of developing life-threatening complications such as Stevens-Johnson syndrome or toxic epidermal necrolysis [13, 57].

Symptoms and management

The clinical presentation of platinum induced hypersensitivity reactions can vary both in terms of clinical

manifestations and the time of symptoms onset in relation to the drug administration. Most patients present cutaneous manifestations such as pruritus, urticaria, flushing or angioedema [40]. Other clinical manifestations such as dyspnoea, bronchospasm, diarrhoea, nausea, fever, chills and cardiovascular manifestations that may include arrhythmias and blood pressure variations have also been described [51, 63]. Respiratory symptoms are second to cutaneous manifestations in frequency, while cardiovascular symptoms are less common, but more severe [9]. Symptoms are common for all platinum derivatives. However, oxaliplatin may display atypical presentations, including dyspnoea and hypoxia in the absence of bronchospasm, chills, fever, abdominal, back or chest pain during infusion, haematuria, haematemesis, epistaxis disorientation and altered mental status [4]. Dysesthesia with laryngeal spasm is a neurotoxic effect of oxaliplatin, and it should be distinguished from an allergic reaction [38].

Clinicians and patients have to be aware of the possibility of allergic reactions. Patients need to be counselled about the risk of hypersensitivity reactions and taught to distinguish the signs and symptoms and report them to the treating physician. An initial risk assessment must be carried out at treatment initiation and during the treatment. Patients at risk for platinum HSR should be monitored by experienced healthcare professionals, able to recognize and manage potentially life-threatening allergic reactions.

There are various classification systems to grade hypersensitivity reactions; however, the National Cancer Institute Common Terminology Criteria for Adverse Events v 4.03 is more frequently used [11]. In the face of an allergic reaction, treatment involves early diagnosis and cessation of drug administration. A quick evaluation of the patient's airways, breathing, circulation and consciousness are mandatory. Venous access must be ensured. For patients with anaphylaxis, epinephrine must be administered without delay. Oxygen must be administered if needed. Patients with hypotension must be placed in the Trendelenburg position. Fluid resuscitation must be initiated with the rapid administration of 1 - 2 litres of normal saline. Atropine is indicated for the treatment of bradycardia. Antihistamines improve symptoms such as pruritus and angioedema, but have no life-saving effect. Vasopressors may be needed in cases where epinephrine and fluid resuscitation failed. Corticosteroids are efficient in preventing delayed reactions, but their therapeutic effects occur after a few hours and therefore are inefficient in the management of acute severe allergic reactions. Vital signs and recurrence

symptoms must be monitored post-reaction, and a 24 h close observation is recommended [22, 66, 80].

Desensitisation

History of platinum related hypersensitivity reactions is a challenging issue that treating physicians have to surpass. The main predicament is whether platinum-based chemotherapy should be discontinued or not. After a platinum-related HSR, physicians have five possible options: premedication, prolonged infusion time, changing the platinum derivative, desensitisation and permanently discontinuing platinum derivatives. When selecting the best treatment plan, the severity of the allergic reaction is a crucial deciding element. Other confounding factors are treatment setting, palliative or curative treatment, the possible clinical benefit of continuing the platinum compound and the availability of other viable treatment options.

For patients with mild to moderate reaction, rechallenge with additional premedication, corticosteroids, anti-histamines, or changing the platinum compound is an option; however, with limited efficiency, as cross-reactivity between platinum derivatives has been described and more intensive premedication still carries a high risk of severe allergic reactions [4, 24, 82]. Some studies have shown that prolonged infusion time might be an efficient option for some patients allowing treatment continuation and reducing further allergic reactions [35, 60, 66]. O'Cearbhaill *et al.* validated a prolonged 3-hour infusion protocol for carboplatin, compared to the standard 30 min infusion, coupled with rigorous premedication, which led to an 18% reduction of hypersensitivity reactions [56].

Recurrent reactions despite premedication or longer infusion time and serious initial allergic reactions oblige the use of desensitization protocols. First described for penicillin [72], desensitization is used in a wide array of clinical scenarios. Desensitization is the process by which the immune response is altered, in order to induce temporary tolerance to the targeted drug. During desensitization, the administration of subthreshold, incremental, antigen doses promotes the transduction of predominantly inhibitor signals, by abolishing intracellular calcium influx, which leads to increasing unresponsiveness to specific antigens [68]. Numerous desensitization protocols have been successfully used for various chemotherapy agents, including platinum derivatives, allowing for treatment continuation. Most desensitisations use standardized multi-step administration protocols that allow the administration of the full therapeutic dose, usually in a short time interval of 4 - 12 hours [57]. Table I encompasses the main desensitization protocols used for the treatment of platinum hypersensitivity reactions.

Table I

Published desensitization protocols for platinum hypersensitivity

	Chemotherapy	Patients	Protocol	Duration (hours)	Setting	Skin testing	BTR (%)	Success rate (%)
Castells <i>et al.</i> [15]	Carboplatin Cisplatin Oxaliplatin	64	12 step, 3 dilutions from 1:100 - 1:1	5.8	ICU 1 st administration; Outpatient afterwards	Yes	33	100
Kuo <i>et al.</i> [34]	Carboplatin Oxaliplatin	10	12 step, 3 dilutions from 1:100 - 1:1	5.8	Outpatient	Yes	16	70
			5 step dilutions from 1:10000 - 9:10	2 - 5				
Abe <i>et al.</i> [1]	Cisplatin	3	6 step dilutions from 1:1000-1:1	12	N/A	No	33	66
Altwerger <i>et al.</i> [2]	Carboplatin	129	4 steps dilutions from 1:1000 - 1:1	3.5	Inpatient non-ICU ICU 1 st administration: 1 patient	Yes	27.1	87.6
Brault <i>et al.</i> [5]	Carboplatin Oxaliplatin Cisplatin	30	12 steps dilutions from 1:100 to 1:1	3	N/A	Yes	36.6	86.6
Hesterberg <i>et al.</i> [26]	Carboplatin	30	8 step, 2 dilutions from 1:10 to 1:1	6.35	Inpatient non-ICU	Yes	17.9	99
			10 step dilutions from 1:100 to 1:1	11.05				
Wang <i>et al.</i> [79]	Carboplatin Oxaliplatin	109	12 step, 3 dilutions from 1:100 - 1:1 8 step 1:10 to 1:1	5.8 6.35	Inpatient non-ICU	Yes	N/A	N/A
Bruchim <i>et al.</i> [7]	Carboplatin	49	3 step dilutions from 1:1000 to 1:1	6/15.5	N/A	Yes	20.4	89.7
Caiado <i>et al.</i> [8]	Carboplatin Oxaliplatin Cisplatin	136	12 step: 3 dilutions from 1:100 - 1:1	6	Outpatient	Yes	16.3	93%
Castells <i>et al.</i> [13]	Carboplatin	31	12 step, 3 dilutions from 1:100 - 1:1	5.8	Inpatient non-ICU ICU 1 st administration	Yes	35.4	100
Choi <i>et al.</i> [17]	Carboplatin	8	24 steps, 4 dilutions from 1:1000 to 1:1	96	Inpatient non-ICU	Yes	0	100
Chung <i>et al.</i> [18]	Carboplatin Cisplatin Oxaliplatin	36	12 steps, 1 dilution	4.2	Inpatient non-ICU	Yes	16.7	100
Confino-Cohen <i>et al.</i> [19]	Carboplatin	23	4 step, 4 dilution from 1:1000 to 1:1	6	N/A	Yes	5	95
Cortijo-Cascajares <i>et al.</i> [20]	Oxaliplatin	21	14 step, 13 dilutions from 1:100 to 1:1	3 - 4	N/A	Yes	11	100
Gastaminza <i>et al.</i> [23]	Carboplatin Oxaliplatin	4	5 step, 5 dilutions from 1:10000 to 1:1	2	Inpatient non-ICU ICU 1 st administration	Yes	25	75
Gomez <i>et al.</i> [25]	Carboplatin	7	4 steps, 4 dilutions from 1:1000 to 1:1	2	N/A	Yes	28.5	85.7
Jones <i>et al.</i> [29]	Carboplatin Cisplatin	5	4 steps, 4 dilutions from 1:1000 to 1:1	1.5	Inpatient non-ICU	Yes	40	60
Kang <i>et al.</i> [30]	Carboplatin Oxaliplatin Cisplatin	36	12 step, 3 dilutions from 1:100 - 1:1 16 step, 4 dilutions 1:1000 - 1:1	7.8	Inpatient non-ICU	Yes	44.8	91.6
Kendirlinan <i>et al.</i> [31]	Carboplatin Oxaliplatin Cisplatin	22	12 step, 3 dilutions from 1:100 - 1:1	N/A	Inpatient non-ICU	Yes	50	90.9
			16 step, 4 dilutions 1:1000 - 1:1	N/A				
Lee <i>et al.</i> [37]	Carboplatin	31	12 step, 3 dilutions from 1:100 - 1:1	3.8	Inpatient non-ICU ICU 1 st administration	Yes	30.5	100
Lee <i>et al.</i> [36]	Carboplatin	10	12 step, 3 dilutions from 1:100 - 1:1	5.82	Inpatient non-ICU ICU 1 st administration	Yes	40	100

	Chemotherapy	Patients	Protocol	Duration (hours)	Setting	Skin testing	BTR (%)	Success rate (%)
Li <i>et al.</i> [39]	Carboplatin Cisplatin	18	4 step, 1 dilution	1.5 - 2.25	Outpatient	No	32	100
Madrigal-Burgaleta <i>et al.</i> [41]	Oxaliplatin Carboplatin	11	10 steps, 3 dilutions	4.25	ICU	Yes	6	100
Madrigal-Burgaleta <i>et al.</i> [42]	Carboplatin Oxaliplatin Cisplatin	104	10 steps, 3 dilutions	4.5	Inpatient non-ICU ICU 1 st administration	Yes	12	100
Markman <i>et al.</i> [47]	Carboplatin Cisplatin	4	4 steps, 4 dilutions from 1:1000 to 1:1	1.5	N/A	Yes	0	100
Park <i>et al.</i> [59]	Oxaliplatin Cisplatin	12	11 step, 4 dilution from 1:1000 to 1:1	6.38	N/A	Yes	42.8	100
Pérez-Rodríguez <i>et al.</i> [61]	Oxaliplatin Carboplatin	46	9 steps, 1 dilution	3.48	Outpatient	Yes	5.3	95.6
Robinson <i>et al.</i> [64]	Carboplatin Cisplatin	10	4 steps, 4 dilutions from 1:1000 to 1:1	4	N/A	Yes	0	100
Rose <i>et al.</i> [65]	Carboplatin	33	4 steps, 4 dilutions from 1:1000 to 1:1	16.5	Inpatient non-ICU	No	22	78
Syrigou <i>et al.</i> [73]	Oxaliplatin	3	13 steps, 7 dilutions from 1:100000 to 1:1	8	Outpatient	Yes	0	100
Takase <i>et al.</i> [74]	Carboplatin	20	4 steps, 4 dilutions from 1:1000 to 1:1	4	Inpatient non-ICU	No	15	95
Toyohara <i>et al.</i> [75]	Carboplatin	5	4 steps, 4 dilutions from 1:1000 to 1:1	5	Inpatient non-ICU	No	20	80
Vetter <i>et al.</i> [77]	Carboplatin Cisplatin	48	4 steps, 1 dilution	2.25	Outpatient	No	65	96.6
			16 steps, 3 dilutions from 1:100 to 1:1	14	Inpatient			
Vidal <i>et al.</i> [78]	Carboplatin	8	16 steps, 1 dilution	4.5	Outpatient	Yes	12.5	100
Wong <i>et al.</i> [80]	Oxaliplatin	48	13 steps, 3 dilutions from 1:1000000 to 1:10	4.7 - 16	N/A	Yes	37.5	100

BTR: breakthrough reactions, ICU: intensive care unit, N/A: not available

A recent study by Castells *et al.* [15] used a standardized 12-step desensitization protocol in 98 patients; among these, 64 had platinum-related allergic reactions. Subjects received premedication followed by the administration of three solutions in twelve consecutive steps. Total desensitization time was of 5.8 hours. The first desensitization was administered in an intensive care unit while the others were administered in an outpatient setting. Of the 413 desensitizations performed, 94% lead to no or mild reactions. Most reactions occurred during the first two desensitizations, more frequently during the final step of the protocol; however, all reactions were less severe than the initial allergic reaction. In patients presenting with HSR related symptoms, despite desensitization, the addition of 325 mg of acetylsalicylic acid and 10 mg of montelukast two days prior and on the desensitization day led to significant symptom control [6].

Altwerger *et al.* conducted an analysis encompassing 129 patients who received a total of 788 desensitization cycles for carboplatin. A four-step desensitization protocol was used, and total administration time was of 3.5 hours. Two patient groups underwent desensitization, patients with prior HSR to carboplatin (43.4%) and patients with positive carboplatin skin tests. Patients

with positive skin tests presented more HSR during desensitization than those with a history of HSR. Most patients received their desensitization in a non-intensive care inpatient unit, 87.6% completed their desensitization, with an average of 6.1 desensitization cycles administered. Most patients had no or mild reactions during desensitization, 9% presented moderate to life-threatening events, and one death occurred due to a severe anaphylactic reaction [2].

In patients with a history of platinum induced allergic reactions, skin testing was advocated as a useful tool in predicting future reactions and selecting patients for further platinum reexposure. However, the use of skin testing in an everyday clinical setting remains controversial as the sensitivity of skin tests for platinum salts varies across different studies, from 66% to 80 - 88%, in some studies as low as 27% for oxaliplatin [9] and multiple tests are frequently necessary for adequate risk stratification. Hesterberg *et al.* used skin testing for selecting the desensitization protocol in patients with carboplatin HSR. Patients with negative skin tests received a more rapid 8 step protocol, while those with positive tests had a longer 10 step desensitization protocol. Subjects with negative skin tests within three months of the HSR did not display hypersensitivity symptoms during desensitization and

remained negative. Patients with testing performed at more than 9 months after HSR tested positive before the second desensitization cycle and had subsequent reactions even during the prolonged desensitization protocol [26].

Skin testing, however, may be effective in selecting patients with a very low risk for further allergic reactions. A three-step risk stratification protocol was analysed in a retrospective analysis conducted by Wang *et al.* in 142 patients with carboplatin and oxaliplatin HSR. Patients with negative tests undergone 8-step desensitization regimen with repeated skin testing before each cycle. Patients that remained negative after the third test continued their treatment schedule without desensitization. 77.3% for carboplatin and 88.9% for oxaliplatin, of the patients that continued outpatient treatment without desensitization, had no additional HSR related symptoms. However, patients with severe initial HSR, even though they qualified for treatment without desensitization, were not referred to outpatient infusions [79]. Caiado *et al.* searched for potential biomarkers that may aid in selecting patients at risk for allergic reactions during desensitization by analysing 1471 desensitizations in 272 patients. On multivariate analysis, a total Ig E level greater than 100 U/mL and more than ten previous platinum administration were found as significant risk factors for further HSR during desensitizations with an OR of 8.24 and 4.11, respectively [8].

Conclusions

Platinum derivatives are essential chemotherapeutic agents, and they represent the treatment mainstay in a variety of cancers. However, hypersensitivity reactions greatly impair the administration of platinum agents, especially in patients with a history of atopy, a large platinum-free interval and patients with more than seven administrations. Continuation of platinum-based chemotherapy after an initial allergic reaction is highly unsafe as hypersensitivity reactions are potentially fatal complications. Also, due to cross-reactivity, switching platinum compounds may not be the preferred option. Therefore, in patients with limited alternative treatment options or patients with cancers where platinum chemotherapy is essential, desensitization protocols are viable options. Various protocols have been published, and they allow treatment completion with a good safety and efficacy profile. Desensitizations should be administered in a specialized ward with personnel trained in desensitization administration and management of severe hypersensitivity and anaphylaxis as there remains a risk for potentially life-threatening allergic reactions. Further research is needed in selecting patients suitable for desensitisation, identifying those who are at risk and should receive desensitisation before an allergic reaction and optimising desensitisation protocols.

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Conflict of interest

The authors declare no conflict of interest.

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