

## Review Article

# Platinum hypersensitivity and desensitization

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### Abstract

Platinum agents are drugs used for various types of cancer. With increased frequency of administration of platinum agents, hypersensitivity reactions appear more frequently, occurring in over 25% of cases from the seventh cycle or second line onward. It then becomes difficult to conduct treatment using these agents. Various approaches have been investigated to address hypersensitivity reactions to platinum agents. Desensitization, which gradually increases the concentration of the anticancer drug considered to be the antigen until the target dosage, has been reported as being particularly effective, with a success rate of 80–100%. The aims of this paper are to present the current findings regarding hypersensitivity reactions to platinum agents and to discuss attempts of using desensitization against hypersensitivity reactions worldwide.

**Key words:** platinum, hypersensitivity, desensitization

### Introduction

Chemotherapy including platinum agents is effective against a large number of cancers and is used widely. By forming crosslinks with DNA bases within cancer cells, platinum agents act to inhibit DNA replication; this leads to suppression of division and proliferation of cancer cells, thus killing these cells.

Cisplatin, a first-generation platinum agent, is a non-natural compound that was serendipitously discovered during a work conducted by Rosenberg et al. (1). For its efficacy, it is recommended that treatment be discontinued after a maximum of six cycles when treating non-small cell lung cancer (2,3). On the other hand, some Phase 3 trials have been conducted using this agent for gastric cancer, in which it has been administered continuously until progression (4,5), with a reported median number of 4 cycles and a maximum of 11 cycles (4).

Carboplatin, a second-generation platinum agent, is administered depending on kidney function because it can be administered to patients with reduced kidney function. Additionally, as it does not require large-volume transfusion, it can be administered to outpatients and is used in place of cisplatin for the treatment of many types of cancer. In ovarian cancer, chemotherapy including carboplatin is used as a standard primary treatment. It has been reported that, in cases in

which relapse occurs >6 months following this primary treatment, re-treatment with carboplatin-containing chemotherapy yields favorable results (6,7).

Oxaliplatin, a third-generation platinum agent, is an integral drug used for colorectal cancer (8–11) and pancreatic cancer (12). It is administered either until treatment discontinuation due to toxicity or is continually administered until progression. One of the characteristics of oxaliplatin that differentiates it from other platinum agents is an increased frequency of cold-sensitive dysesthesia and peripheral neuropathy, which may lead to discontinuation of treatment (10).

Clinicians occasionally encounter hypersensitivity reactions (HSRs) to platinum agents. Hypersensitivity to a chemotherapeutic agent is defined as unexpected reactions that cannot be explained by the known toxicity profile of the drug (13). It has been known that, as the administration of platinum agents becomes more frequent, the incidence of HSRs will also increase (14). HSRs can lead to life-threatening conditions and thus require immediate treatment. Consequently, when patients have experienced HSRs, clinicians must choose, based on their consideration of the risk of causing even more serious adverse reactions or anaphylaxis, whether to continue with the same treatment or to suspend treatment and

to search for other treatment options, although it is possible that chemotherapy with platinum agents is the only effective treatment option. In recurrent ovarian cancer in particular, carboplatin is associated with the 'platinum-sensitivity relapse' concept and oxaliplatin is used as the key drug for adjuvant therapy, first-line therapy and second-line therapy for colorectal cancer. As continued re-administration of these platinum agents contributes to prolonged survival periods, clinicians contemplate rechallenge with these platinum agents.

Approaches to address HSRs include reducing the infusion rate (15), administering premedication (16), switching to a different platinum agent (17,18) and skin testing (19). However, in particular, desensitization is an effective method (20).

The aims of this paper are to present the current findings regarding HSRs to platinum agents and to discuss attempts of using desensitization against HSRs worldwide.

## Mechanism

Based on their mechanism of development, HSRs are classified into either allergic reactions, which involve an immunological mechanism, or non-allergic cytokine release syndrome (21). Additionally, the type of allergic reaction can be further classified into four categories (Table 1).

Allergic reactions and anaphylaxis are caused by an immunological mechanism and HSRs occur within a relatively short time of the administration of the drug. Such HSRs are of the 'immediate type' and are classified as Gell and Coombs Type I allergies (21,22). On the other hand, cytokine release syndrome occurs due to the binding of the administered drug to circulating immune cells, such as monocytes and macrophages, causing the release of cytokines (23).

Although the mechanism by which platinum agents cause HSRs has not yet been clearly elucidated, they are generally reported as immediate Type I allergies (24). In Type I allergies, mast cells and basophils react via IgE and release chemical messengers such as histamine, leukotrienes and prostaglandins, which in turn cause a variety of symptoms. Among allergic reactions, those with the most severe and rapid onset and fatal large-scale or systemic reactions are called anaphylaxis. Although anaphylaxis is rare, its onset is life-threatening and

necessitates that careful attention and appropriate measures should be taken (25).

One reason why Type I reactions are believed to be closely involved in HSRs is that there exist reports stating that skin testing is effective in diagnosis and prediction of HSRs to platinum agents (19,26,27). Such methods include prick testing, where the skin is pricked with a needle lightly enough such that bleeding does not occur, and then, an antigen-containing fluid is applied at the prick site. Another method is intradermal testing, where 0.02 ml of a diluted antigen-containing fluid is injected into the skin. Some studies have been conducted using intradermal testing alone (26,27); however, other studies have been performed with the safer skin prick testing; these studies then used intradermal testing for the negative cases (19,28), with the latter approach being used in recent studies. Markman et al. (26) reported skin testing as a useful method for predicting HSRs, with anaphylaxis occurring in six of seven skin test-positive patients when retreated with carboplatin, resulting in a negative predictive value of 98.5%. Zanotti et al. (27) also reported that, in a study of 47 patients, those who were negative for the intradermal reaction had a reduced risk of developing HSRs to carboplatin and had milder reactions even when HSRs did occur. However, it was found that the false-negative rate was ~8% (26,29), indicating the limits of the test or the possibility that other mechanisms may contribute to HSRs. At present, skin testing of anticancer drugs as sensitivity tests in patients with no medical history of HSRs to platinum agents is thought to be unethical due to adverse events such as irritant reactions and is not conducted routinely (30).

Rarely, case reports present the possibility that cytotoxic (Type II) hypersensitivity and immune complex (Type III) hypersensitivity contribute to HSRs to platinum agents (15,31–34). Additionally, it has been suggested that cisplatin and carboplatin also induce Type IV hypersensitivity through delayed T-cell sensitization (14). Santini et al. (35) reported that 20 min following the administration of oxaliplatin, cases with chills, stomach pain, diarrhea and fever showed increases in TNF- $\alpha$  and IL-6, suggesting that oxaliplatin may act like a superantigen to stimulate the release of these cytokines. Similar findings have been reported in some other papers (36,37).

In other words, because the pathologies of HSRs to platinum agents are not limited to Type I allergic reactions, clinicians must be

**Table 1.** Classification of allergic reactions (Gell and Coombs)

Type of HSRs	Antibody	Antigen	Mediators	Skin test	Symptoms
I Immediate type	IgE	Exogenous antigen e.g. house dust, pollen, drug, mite	Histamines Leukotrienes Prostaglandins Platelet activating factor etc.	Immediate	Urticaria Angioedema Bronchospasm Anaphylaxis
II Cytotoxic type Cytolytic type	IgG IgM	Exogenous antigen (hapten) e.g. drug Cell- or matrix- associated antigen	Complement		Hemolytic anemia Thrombocytopenia Goodpasture syndrome
III Immune complex type	IgG IgM	Exogenous antigen e.g. drug, bacillus Autoantigen e.g. DNA	Complement Lysosomal enzyme	Delayed (h)	Serum sickness
IV Delayed type Cellular immunotype	Sensitized T lymphocytes	Exogenous antigen e.g. bacillus, drug Autoantigen	Cytokines	Delayed (days)	Contact dermatitis

HSR, hypersensitivity reactions.

attentive to the possibility of a reaction occurring well after the administration of the agent (38–41).

**Incidence**

Following the finding that immediate type hypersensitivity and asthma were occurring in workers at platinum refinement plants who repeatedly inhale platinum-containing dust (42), HSRs due to the use of anticancer agents have been reported since the 1970s (43). The incidence according to each agent is outlined in Table 2.

It is known that the HSR frequency increases with the number of carboplatin administrations (44,45). It has been reported that HSRs occur in 1% of cases in which carboplatin is administered for five or fewer cycles (45), but they occur in as many as 27% of cases in which more than seven cycles are administered (44). Additionally, it has been reported that HSRs occur in 44% of cases using second- and third-line therapies (46). In cases in which the clinician has a high probability of encountering HSRs, such as in ovarian cancer patients, it is expected that HSRs will be induced after retreatment with a carboplatin-containing regimen for relapses occurring after an interval of 6 or more months from the completion of primary therapies that incorporated carboplatin, hindering further treatment. Furthermore, HSRs have been reported in intraperitoneal administrations as well as transvenous administrations (47).

Similar to carboplatin, it is known that the HSR frequency increases with the number of cisplatin administrations (48,49); however, there are few reports of the frequency of HSRs, none of which are recent, with estimations ranging from 1 to 14% (50). Additionally, combination with radiation therapy increases the incidence of HSRs (51). Gralla et al. (49) reported no HSRs with up to five cycles of therapy, and yet, they reported that the incidence increased rapidly when the number of cycles reached six and above. However, there are few cases of more than six cycles of cisplatin being used for many types of cancer at present, and thus, HSRs may be encountered less frequently in cases of cisplatin administration.

When oxaliplatin was clinically adopted, the incidence of HSRs to this agent was found to be very low at 0.55% (52). However, reports of the HSR onset have increased with oxaliplatin use following the finding that oxaliplatin is effective as adjuvant chemotherapy for colon cancer as well as for unresectable or recurrent colon cancer, with a reported recent incidence of 10–25% (32,53–60). Although the majority of these were mild-to-moderate reactions, severe toxicity (Grade 3/4) cases occurred at a rate of ~1.6–7.3%, and thus, caution is warranted. The median number of administrations before the onset of an HSR is ~7–9, and similar to the other platinum agents, use of six or more cycles has been found to increase the HSR incidence. Kim et al.

(56) reported that the median time to the onset was 70 min from starting administration, and Polyzos et al. (32) reported that more severe HSRs occurred within 5–10 min from starting administration.

**Risk factors**

It is known that, in general, the incidence of HSRs to platinum agents increases as the number of administrations increases (21).

The reported risk factors for HSRs to carboplatin include age <70 years (61); a history of allergies to environmental stimuli or drugs (44,62); administration with carboplatin at 650 mg or more (63); and a long platinum-free interval (62–64). However, currently, studies have not consistently identified any risk factors.

Recently, Moon et al. (65) reported a mutation in the tumor suppressor gene BRCA1/2 as a risk factor for HSRs. According to their investigation, of 29 patients who either developed an HSR or had a history of HSRs, 27 had mutations in the BRCA gene, while of 31 patients with no mutations in the BRCA gene, only 2 patients developed HSRs. Consequently, it is possible that genetic mutations have some effect on the immune response.

Additionally, it has been reported that the combined use of liposomal doxorubicin and carboplatin is associated with a reduced HSR incidence rate when compared with combinations with paclitaxel (5.6 vs. 18.8%) and carboplatin alone (0 vs. 30%), which suggests the possibility that liposomes have some impact on immune cells. However, the underlying mechanism for this remains unclear (66,67).

Schwartz et al. (64) reported that the risk of a severe HSR to carboplatin was higher in the group in which the platinum-free interval was 2 years or more than in the group in which the interval was less than a year (47 vs. 6.5%), although these results require further verification.

Although there are a number of reports that have investigated the risk factors for the onset and severity of HSRs to oxaliplatin, as with carboplatin, a clear theory remains to be established (56–58,68,69). Kim et al. (56) suggested three risk factors for the onset of HSRs to oxaliplatin, including young age, female gender and use of oxaliplatin as a second-line or higher therapy. Female gender was also reported to be a risk factor for HSRs in a multivariate analysis by Parel et al. (60). Additionally, the total dose of oxaliplatin administered (57) and oxaliplatin-free interval (69) have been reported to be associated with HSRs, although further verification of these results is required.

**Symptoms and treatment**

The clinical manifestations of HSRs are both diverse and unpredictable. Cutaneous manifestations (pruritus, urticaria, facial flushing, angioedema, palmar erythema, erythematous rash), fever and/or shaking chills, gastrointestinal manifestations (abdominal pain, diarrhea, nausea), respiratory manifestations (dyspnea, bronchospasm) and circulatory manifestations (heart rate and blood pressure alterations) are generally found (13). However, cutaneous symptoms are found in 80–90% of patients with HSRs (25,70). Additionally, although most manifestations remain only mild to moderate, there are reports of manifestations escalating into severe and fatal manifestations (71).

The severity of symptoms is generally evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 (Table 3).

Treatment of HSRs first involves early perception of changes in the patient’s condition, and the administration of drugs is then ceased, and

**Table 2.** Incidence and severity of hypersensitivity to platinum drugs

Drug	Incidence (%)	Severe HSR incidence (%)	Median cycles of initial onset	Incidence (%)
Cisplatin	1–14	–	6	<5 cycles 0
			>6 cycles	24
Carboplatin	1–44	2	8	<6 cycles 3.4
			>7 cycles	27
Oxaliplatin	10–25	1.5–7	8	Front-line 9
			Second-line or higher	24

**Table 3.** National Cancer Institute—Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Adverse event	Grade				
	1	2	3	4	5
Allergic reaction	Transient flushing or rash, drug fever <38°C (<100.4°F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDs, narcotics); prophylactic medications indicated for ≤24 h	Prolonged (e.g. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g. renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Anaphylaxis	–	–	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 h	Prolonged (e.g. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g. renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilatory support indicated	Death

NSAIDs, non-steroidal anti-inflammatory drugs.

the infusion is then replaced with physiological saline. After a rapid evaluation of the patient's circulation, airway, breathing, state of consciousness and skin, oxygen is provided as required, and the venous administration of antihistamines and glucocorticoids or the rapid administration of epinephrine is provided for anaphylaxis or other severe cases (32). Antihistamines alleviate symptoms such as itching, urticaria and angioedema but have no life-saving effect (72). Glucocorticoids may also alleviate delayed reactions, but the therapeutic effects occur after some hours, and these drugs also have no life-saving effect (72). Epinephrine is used as the primary treatment, particularly for anaphylaxis, and an intramuscular injection of 0.1% (0.01 mg/kg) epinephrine (with a maximum of 0.5 mg for adults) is given immediately to the anterolateral side of the central thigh whenever there is a diagnosis or strong suspicion of anaphylaxis (73).

Although symptoms usually occur during or within a few hours of administration, the symptom onset can occur 1–2 days after administration in rare cases, and hence, it is critical to inform patients of this possibility (22). Additionally, extra attention should be paid to anaphylaxis cases in which biphasic anaphylaxis may occur several hours after cessation of treatment and resolution of symptoms (74).

The diagnosis of HSRs to platinum agents depends greatly on the patient's clinical course but is exceptionally difficult because of many confounding factors. First, patients receiving cancer therapy are prescribed many drugs that can cause HSRs. Second, it is possible that the cancer itself acts directly on mast cells to produce similar symptoms to those of an HSR. Third, several epidemiological studies have found that certain cancers have been shown to increase the risk of allergies (75). Because platinum agents are invaluable drugs in a number of cancers, and, unlike other drugs, they cannot be easily replaced, clinicians must evaluate the clinical course of

HSRs very carefully to analyze the possible link to platinum agent use. If possible, diagnosis may be made based on the results of skin or challenge testing (76).

When the clinician judges that an HSR to a platinum agent has occurred, but the prospect of altering the current treatment is unlikely because it has a firm basis and is effective, they must search for a treatment option that can be safely performed in cancer patients with allergy (75).

## Desensitization

Since the report of desensitization to penicillin, the desensitization of various agents has been studied (77,78). Desensitization is the process in which the concentration of an anticancer drug acting as an antigen is increased in a slow and step-wise manner to induce a temporary tolerization state toward the drug, until the target dose is reached. It is also a useful approach for HSRs to platinum agents. No standardized protocol for desensitization has been established, and protocols differ by institution, with some even implementing it in outpatients (Table 4).

Although the mechanism of desensitization has not been fully understood, one hypothesis states that the internalization of antigen-specific IgE plays an important role (79–81). This has been tested through basic researches, and various *in vitro* and *in vivo* results have been reported (82,83). High-affinity IgE receptors on the surface of mast cells and basophils (FcεRI) act as key inducers of allergic reactions. When re-exposed to the causative agent, drug-specific IgEs bound to FcεRI bind to the drug and, through crosslinking of IgE, activate intracellular signaling to release chemical mediators such as histamine, leukotrienes, prostaglandins and cytokines in mast cells and

**Table 4.** Main desensitization protocols for platinum hypersensitivity

		Patients	Premedication-dose-route	Steps	Duration	Completion rate
Carboplatin	Confino-Cohen et al. (107)	20	Nothing Only antiemetics containing dexamethasone	From 1:1000 to 1:1 in four steps	6 h	95% of patients 99% of procedures
	Hesterberg et al. (89)	30	Fexofenadine 180 mg p.o. and/or desloratadine 5 mg p.o. Antiemetics containing dexamethasone 10 mg p.o.	Skin testing negative From 1:10 to 1:1 in eight steps Skin testing positive From 1:100 to 1:1 in 10 steps	6.35 and 11 h	97% of patients 99% of procedures
	Rose et al. (108)	33	Dexamethasone 20 mg p.o. or i.v. 6 h before Dexamethasone 20 mg i.v. and Diphenhydramine 50 mg i.v. 30 min before	From 1:1000 to 1:1 in four steps	16.5 h	79% of patients
	Lee et al. (87)	31	Diphenhydramine 25 mg i.v. Famotidine 20 mg i.v. or ranitidine 50 mg i.v. Lorazepam 1 mg (as needed for anxiety)	From 1:100 to 1:1 in 12 steps	5.8 h (inpatient) and 3.8 h (outpatient)	100% of patients and procedures 85% without symptoms
	Castells et al. (70)	60	Diphenhydramine or hydroxyzine 25 mg p.o. or i.v. Famotidine 20 mg i.v. or ranitidine 50 mg i.v. Lorazepam 0.5–1 mg p.o. or i.v. (as needed for anxiety)	From 1:100 to 1:1 in 12 steps	5.8 h	100% of patients and procedures 67% of procedures without symptoms
	Takase et al. (88)	20	Dexamethasone 24 mg i.v. ranitidine 50 mg i.v. Diphenhydramine 50 mg p.o.	From 1:1000 to 1:1 in four steps	4 h	80% of patients 95% of procedures 81% of procedures without symptoms
	Oxaliplatin	Lee et al. (92)	38	Chlorpheniramin 20 mg i.v. Hydrocortisone 100 mg i.v.	From 1:100 to 1:1 in 12 steps or from 1:10 000 to 1:1 5 steps	5.8 h or 8 h
	Cortijo-Cascajares et al. (91)	21	Corticosteroids: 1 mg/kg/day; Ranitidine: 300 mg/day; Cetirizine 20 mg/day; Montelukast: 10 mg/day the night before and 30 min before infusion	Total dose administered in an average of 14 steps	3–4 h	100% 89% of procedures without symptoms

i.v., intravenous; p.o., per orum.

basophils. These chemical mediators can induce vasodilation, bronchoconstriction and cardiac rate disturbances (84,85). In desensitization therapy, increasing doses of the antigen are administered at fixed intervals. Using this procedure in mouse bone marrow-derived mast cells sensitized to IgE specific to antigens such as dinitrophenyl and ovalbumin, the release of chemical mediators was suppressed (82). The production of cytokines related to delayed onset reactions, like IL-6, was also suppressed. This may explain why there are few reports of delayed onset reactions in desensitization (82).

The most comprehensive study of desensitization is that conducted by Castells et al. (70), which reported rapid desensitization in 98 patients to various drugs over 12 stages. Among these subjects, 65 patients had ovarian cancer, and 59 were desensitized to carboplatin. Three different concentrations of the solution were prepared and administered at four different infusion rates, with an administration time of 15 min for each step, except for the final step. As a result, among cases that underwent desensitization, HSRs occurred in 33% of cases. Nonetheless, it was reported that most of these were mild

reactions and less severe than initial HSRs, and HSRs occurred in 51% of cases during the final step. Regarding the treatment of these HSRs, one patient required epinephrine; however, all the cases completed the administration of carboplatin following recovery from their HSRs through appropriate medical treatment.

Furthermore, the same group reported alleviation of symptoms in 12 of 14 patients who had HSRs during desensitization, and these patients were prescribed 325 mg of acetylsalicylic acid, a prostaglandin blocker, and 10 mg of montelukast, a leukotriene blocker, both were administered 2 days prior to and on the day of desensitization. In 7 of these 12 patients, symptoms disappeared (86). Additionally, the group on acetylsalicylic acid and montelukast showed a significant reduction in symptoms compared with a historical control group using methylprednisolone as premedication (0.5 mg/kg intravenous).

Lee et al. (87) also conducted a 12-step rapid desensitization in 31 cases that had experienced moderate-to-severe HSRs to carboplatin. For safety, the first desensitization was performed in all the cases in an intensive care unit, followed by inpatient or outpatient care.

Administration to 13 outpatients of the 31 cases was made possible by reducing the amount of the solution and using a 3.8 h desensitization protocol. Although HSRs occurred in 15% of the desensitized cases, symptoms improved using, for example, antihistamines, and all cases succeeded in reaching the target dose.

There are only few comprehensive reports from Japan, although Takase et al. reported the use of a four-step, 4 h desensitization protocol in a group of 20 patients. They had a success rate of 80%, and its implementation was comparatively safe, with only a single case experiencing a Grade 3 adverse event (88). The protocol was very simple and rapid, and with the assistance of an allergist, we have conducted similar desensitizations in hospitalized patients at our institution.

Hesterberg et al. (89) modified the desensitization protocol according to the results of skin testing. Interestingly, on investigating the impact of the interval between the onset of initial HSRs and implementation of skin testing, they found that cases negative for the skin test within 3 months of the HSR did not experience HSRs during rapid desensitization. However, of eight patients who had undergone the skin test 9 months after initial HSRs, five showed resensitization during the initial rapid desensitization and tested positive before the second administration, and, even with long-term desensitization protocols, HSRs were found in four cases. By including this skin testing, they concluded that patients who had a long interval between the initial HSR and skin testing and who were converted from a negative to a positive result were at an increased risk of HSRs during the desensitization protocol. On investigating the reproducibility of the above results, 52% of patients who underwent skin testing converted from negative to positive results, and, in 92% of these 'converters,' 6 or more months had elapsed between their first HSR and skin testing (28). Additionally, the frequency of HSRs in the skin testing converter group was also increased, and they suggested that repeated skin testing was important in cases in which considerable time elapsed since their initial HSR.

O'Ceirbhail et al. conducted preventative desensitization over 3 h in 174 patients undergoing the administration of carboplatin for more than eight cycles. This desensitization involved premedication on the day prior to treatment, and on the day of treatment, 1% of the total infusion was administered over 1 h, and then, 9% of the infusion was administered over another hour, with the rest being administered over the third hour (90). Although this was a retrospective investigation, they reported that the 3 h desensitization group had a clear reduction in the incidence of HSRs when compared with the incidence of the group undergoing standard treatment (3.4 vs. 21%), and the median time until the onset of HSRs was increased (16 cycles vs. 9 cycles). Thus, it seems that these types of simple, preventative desensitizations are also worth considering.

There have been few investigations of desensitization to oxaliplatin; however, many of these have a small number of cases. Reports with 20 or more cases are shown in Table 4 (91,92).

Lee et al. (92) conducted a retrospective analysis of the results of 152 patients who had experienced HSRs to oxaliplatin and undergone a premedication protocol with 20 mg of chlorpheniramine and 100 mg of hydrocortisone given 1 h before administration and/or desensitization. The success rate of premedication alone in patients who had severe HSRs was only 22.7%, and this is difficult to endorse. However, the success rate reached 86% when desensitization was conducted, and it is recommended to perform desensitization from initial administration in patients who experienced severe HSRs. Even more interestingly, XELOX regimen with a 3 week interval was found to have a greater number of administrations before the onset of an initial HSR than FOLFOX regimen with a 2 week interval. However, the actual time from the start of treatment to the onset remained the same,

suggesting that rather than the number of administrations, the length of treatment may be important.

The approach for HSRs during desensitization is similar to the approach for HSRs in general; first, treatment is discontinued, and diphenhydramine or hydroxyzine is then administered. If a severe reaction develops, oxygen and inhaled bronchodilators may be given, and H<sub>2</sub>-blockers and glucocorticoids are administered intravenously. When necessary, epinephrine may also be considered (70). After resolution of symptoms, while carefully verifying the safety, treatment may be restarted from where the desensitization process was interrupted, with a reduced infusion rate or a reduced increment of dose.

## Discussion

The time within which HSRs are likely to occur in chemotherapy depends on the drugs used. Although they may occur on the first administration of taxanes, reactions to platinum agents often occur on readministration, and they are thus classified as the late onset (21). On rare occasions, HSRs represent very serious adverse events that can lead to death (93).

Although careful consideration should be given to strategies to respond to HSRs, routine premedication with antihistamines and steroids before starting treatment for HSRs to platinum agents is widely viewed in a negative light (53,94,95). Brandi et al. (53) reported that, even with premedication, five of six patients developed HSRs, and that simple premedication alone is not a sufficient approach. It is also worth considering switching to other platinum agents, and the efficacy of switching to nedaplatin has also been reported in Japan (96,97). However, this cannot be strongly recommended as methods of clinically investigating cross-reactivity between platinum agents are limited and it is difficult to predict safety; most studies have been small-scale and few have been prospective, and fatal cases have been reported (98,99). Skin testing may become false negative under the influence of glucocorticoids to use in an antiemetic drug purpose of chemotherapy and induced as irritation when used extravascularly. Other problems include the risk of inducing anaphylaxis even when used at a low dose and the excessive exposure of medical staff to anticancer drugs. Therefore, skin testing is by no means a requirement (100,101).

Although platinum agent cross-reactivity has been evaluated by means of skin testing and actual switching to other platinum agents, it is difficult to perform skin testing in clinical care settings for the reasons listed above; therefore, the frequency of cross-reactivity has not been clarified (17,30). Although we cannot yet be used in everyday clinical practice, the use of platin-specific IgE and basophil CD203c has been investigated to predict and diagnose HSRs to platinum agents (30,102). Although investigations involved only small groups of patients with HSRs to platinum agents in combination with skin testing in these patients, the sensitivity of carboplatin-specific IgE was 58.3% with a specificity of 100%, while both the sensitivity and specificity of oxaliplatin-specific IgE were 75% (30). Interestingly, 67% of patients with HSRs to oxaliplatin were also positive for carboplatin- and cisplatin-specific IgE despite not having been exposed to either of these. On the other hand, patients with HSRs to carboplatin but without oxaliplatin exposure had a positive rate of 0% for oxaliplatin-specific IgE. The authors stated that oxaliplatin was more immunogenic, and that readily changing to other platinum agents in patients who had HSRs to oxaliplatin should be avoided. CD203c is a specific surface marker on basophils and mast cells and is known to be immediately upregulated on stimulation by an antigen. In an investigation using the basophil surface marker CD203c, a sensitivity of ~55%

and a specificity of ~90% have been reported (103). Although it is too early to determine whether these results are sufficient for clinical use, further progress and development of these tests are anticipated in the future.

Desensitization involves the induction of a state of temporary tolerance by continuous exposure to an agent. However, if exposure to an agent is once lost, this tolerance is also lost. Consequently, the patient must undergo desensitization each time (104). Dependence on time and concentration desensitization appears to be key factors for successful desensitization (105). Although one approach for HSRs during desensitization involves reducing the infusion rate and using a low-gradient concentration change, this increases the infusion time. Such lengthy infusion times on each administration increases the time in which patients and medical staff are under stress, resulting in exhaustion. The search for an appropriate desensitization protocol should be conducted daily and necessitates high-quality, positive experimentation.

Nonetheless, a number of problems remain. HSRs are truly diverse, and patients with HSRs exhibit cutaneous, gastrointestinal, respiratory and circulatory symptoms, which make some cases difficult to diagnose. Additionally, a diagnosis of HSRs to platinum agents is based on clinical course and medical interviews to obtain information regarding any exposure and event up to the time of the onset. However, due to confounding factors such as the effects of advanced age and cranial irradiation on cognitive function and the effects of combination with other agents, there are cases in which it is difficult to make a diagnosis (75,106). Patil et al. (28) stated that, of 39 patients who were previously diagnosed as having HSRs to carboplatin based on the clinical course but were found to be negative in repeated skin testings, 11 (28%) had almost no HSRs during treatment conducted without any desensitization. In other words, it is possible that a certain proportion of patients have had their treatments changed or been desensitized after HSRs, or conditions mimicking HSRs have occurred from some unknown origin. It is therefore necessary to investigate diagnostic criteria using tools other than a patient's clinical course to extract patients with a true HSR to platinum agents.

Additionally, the standards for discontinuing and restarting desensitization following recovery via appropriate treatment of HSRs during desensitization and standards for the protocol for restarting treatment (the infusion rate and concentration) are both required (88). If these standards are entrusted to each clinician, it will likely cause large fluctuations in the completion rate that can be an endpoint of the desensitization protocol. Although Castells et al. (70) restarted treatment even in patients showing severe reactions during desensitization, it is generally appropriate to discontinue treatment for Grade 3 allergic reactions and anaphylaxis. Investigation of infusion times is also necessary. If the frequent of HSRs necessarily causes longer infusion times while using the rapid desensitization protocol, then this may weaken the significance of the rapidity and safety of such approaches.

## Conclusion

When retreating after encountering an HSR, clinicians should act after thorough consideration of the risk of additional adverse events as well as of the efficacy of platinum agents in chemotherapy. Additionally, it is important to adequately explain the situation to patients who will undergo retreatment.

If conducted by medical teams, desensitization is a safe and effective method. The overall survival and quality of life of patients with HSRs to platinum agents can be improved through cooperative

medical practice by teams consisting of not only an oncologist but also an allergist and other experienced medical staff.

## Conflict of interest statement

None declared.

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